PHYSIOLOGY

—

GUENTHER

The Medical Epitome Series

PHYSIOLOGY

A MANUAL FOR STUDENTS AND PRACTITIONERS

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PREFACE TO SECOND EDITION

IT was the aim of the authors in writing this work for its original edition to gather within brief compass those facts of Physiology with which medical students should be familiar in order that they might successfully pursue the more advanced courses of the medical curriculum. It was not the intention to produce a work of originality nor one which should take the place of more elaborate text-books in the instruction of students, but one offering a means of quickly reviewing the essential features of the subject. The demand which exhausted successive printings of the first edition indicates that the work answered its purpose as a brief exposition of Physiology suited to the needs of students and practitioners, and it is hoped that this new and thoroughly revised issue may meet with equal favor.

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PHYSIOLOGY

CHAPTER I

GENERAL INTRODUCTION

Physiology is the science that treats of the functions of normal living matter. As living matter may be either of animals or of plants, so there is a separation of physiology into corresponding divisions—animal and vegetable.

Human physiology consists of those facts of *animal* physiology which have been derived from experiments upon human beings, together with much that has been ascertained for closely allied animals and can be inferred to hold true for man. The chemistry of living things is now a distinct science—*physiological chemistry*—although it was not so formerly. The term *physiology,* derived from the Greek words φύσις and λόγος, is synonymous etymologically in its broadest application and acceptation with *natural philosophy,* and the earliest physiological conceptions were formed in prehistoric times, inseparable as such from the general mass of knowledge which during the course of later centuries grew into theological, scientific, philosophical, and other aggregations of ideas.

The science of physiology as it exists today has been gradually evolved out of the joint labors of thousands and thousands of workers. Of these, there are some that stand preëminent and mark in a way the principal epochs in the history of the subject. In the earliest times among the philosophers who dealt with problems that are now physiological may be mentioned *Empedocles, Hippocrates, Heracleitus,* and particularly *Aristotle* (384–322 B.C.). *Galen* (131 to about 200 A.D.) distinctly recognized the nature and importance of physiology,

His system of medicine, from which the physiology of the time is inseparable, held an almost indisputable sway for nearly thirteen centuries. *Harvey* (1578–1657 A.D.), whose name stands foremost among those of his time, discovered the circulation of the blood. His greatest accomplishment was the establishment of the experimental method in physiology upon a firm basis. With him originated the conception "*omne vivum ex ovo.*" *Haller* (1708–1777 A.D.) was the first to recognize the necessity of bringing together the mass of physiological facts and theories that had arisen during the sixteenth and seventeenth centuries into an independent science. This he did in his *Elementa Physiologiæ Corporis Humani.* *Johannes Müller* (1801–1858 A.D.) was perhaps the greatest physiologist of all times. He impressed upon his science the general form or aspect that it wears today.

The aim of physiology is the investigation of life. The term life is, however, not readily definable. In general, any given piece of matter is said to be alive when it manifests the *fundamental properties* of living things. These properties may be defined as follows:

1. **Irritability** is that property of protoplasm which enables it to undergo characteristic physical and chemical changes when acted upon by certain influences called *stimuli*. Usually there is a liberation of energy in the response out of all proportion to the energy applied in the stimulus.

2. **Conductivity** is that property of protoplasm by virtue of which a condition of activity aroused in one portion of the substance may be transmitted to any other portion.

3. **Contractility** is that property of protoplasm which enables it to change its form when irritated by stimuli.

4. **Nutrition** is that property of protoplasm which enables it to convert dead food material into its own living substance.

5. **Reproduction** is that property of protoplasm which enables it to separate into a number of parts, each of which may develop into the parent form. None of the fundamental properties serve absolutely to distinguish living from dead matter, since all are simulated more or less completely by phenomena in the non-living world.

Life is always associated with a peculiar form of matter called protoplasm, and is never found elsewhere.

Protoplasm has therefore been called the "*physical basis of life.*" It may be defined as the active substance of which living things are composed. It is usually colorless, semifluid or gelatinous in consistency, of greater refractive power than water, and granular in appearance. Consisting largely of water, it nevertheless does not mix with water as long as it is living. Its specific gravity is greater than 1 (paramecium, 1.25), but varies in many organisms by the formation and disappearance of vacuoles.

The *fluid nature* of protoplasm is shown—

1. By the streaming phenomena in plant cells and in the pseudopodia of rhizopods.

2. By its formation into spherical masses whenever it is freed from its cell walls.

3. By the assumption of a spherical form by fluids when embedded in a mass of protoplasm. Granules and all foreign substances lie in a *ground substance*, which at times is perfectly homogeneous, but usually has a structure resembling a network.

Of the many attempts to explain the *finer structure* of protoplasm, that of Bütschli is the most successful. According to this investigator, protoplasm is an emulsion, the vacuoles or globules of which, through mutual pressure, according to well-known mathematical principles, give rise to the appearance of a network. The granules, etc., never lie within the vacuoles, but always between them. Bütschli has imitated in every detail the appearance of protoplasm by artificial emulsions. These were prepared by mixing intimately cane sugar or potassium carbonate with old olive oil. A minute quantity of the mixture, placed in a drop of water under the microscope, showed not only all the peculiarities of the protoplasmic structure, but also spontaneously took on ameboid movements.

Protoplasm is not a chemical but a morphological term— *i. e.*, it does not consist of a definite chemical compound, but of the greatest variety of substances, some of which are the most complicated with which chemists have to deal. It contains *carbohydrates, fats, water, salts,* and always *proteins.* The elements which are present—C, N, H, O, S, P, Cl, K, Na, Mg, Ca, and Fe—are all of low atomic weight. Protoplasm with very few exceptions is divided into microscopic

masses, each of which possesses one or more differentiated portions called a *nucleus*.

Such a Mass with its Nucleus is a Cell.—A cell may be defined as the elementary unit of all organisms, no matter how simple or how complicated they may be. Every organism begins its individual history as a cell separated from a preëxisting organism. From time to time this cell (*ovum, spore,* etc.) divides itself into two or more parts, each of which in due time divides again, the resulting divisions in every case forming complete cells. In the protozoa the daughter cells separate, and each leads an independent existence, but in many-celled animals they remain connected and become dependent upon one another.

An histological differentiation takes place as the animal develops, so that *groups of cells* are formed which are totally different in appearance, and results in tissue and organ formation. They take on different functions, *pari passu,* and one group of cells will perform a certain work for the good of the entire economy. They thus lose their individuality and become dependent upon one another. This is known as the *physiological division of labor.*

The exact molecular structure of living matter is unknown, but there is no doubt that it is of very great complexity. It differs from dead protoplasm in its unstable, labile nature, reacting to an enormous number of substances which are indifferent to dead protoplasm. It manifests a continual tendency to undergo changes, while dead protoplasm, if protected from external agencies, can be kept indefinitely. The nitrogen-containing oxidation products derived from the two are radically different. Those from living matter—uric acid, creatin, adenin, xanthin, guanin, etc.—are all characterized by the possession of the *cyanogen group,* CN. This group is one of great internal energy, so that compounds containing it have a marked tendency to undergo dissociation. This is especially the case in the presence of oxygen. It is a well-known fact that cyanogen compounds also have the *property of polymerization*—that is, of combining with compounds having a structure like their own, so as to form more complex combinations. By such a process living matter becomes less and less stable, until the instability reaches its acme, when the compound undergoes a breaking-down process, resulting

in the formation of simpler, oxidized, more stable bodies. The act of dissociation liberates energy, which appears in the manifestations of life. Pflüger has suggested that in the change from living to dead protoplasm the cyanogen grouping is converted to the inert ammonia grouping by the absorption of water. It is convenient to designate the expression, mass of living matter, by the shorter terms *biogen* or *bioplasm. By biogen is understood the smallest quantity of living matter that can manifest the property of nutrition.*

That part of nutrition designated as *metabolism* is the most characteristic of all the properties of living matter. By it is meant the total series of changes by which substances are built up into living matter (*anabolism*) and again broken down (*katabolism*). Anabolism and katabolism have opposite effects on living matter, but they, nevertheless, go on simultaneously in the same cell, and under normal conditions are always active. When they equal one another the cell is at rest—a condition that has been called *autonomous equilibrium*. If anabolism is in excess of katabolism, the cell increases in bulk or grows, while an excess of katabolism over anabolism will result in atrophy. The relations of anabolism to katabolism may be expressed by the symbol $\frac{A}{D}$. There is no reason to suppose that biogens are all of the same structure; on the contrary, they are probably as numerous as the cells have different functions. Therefore, the relation $\frac{A}{D}$ is more correctly expressed as $\frac{a_1+a_2+a_3+a_4 \ldots}{d_1+d_2+d_3+d_4 \ldots}$, where each of the factors a_1, a_2, a_3 . . . and d_1, d_2, d_3, . . . may vary independently of the others, and within very wide limits, as the case may be.

In any given cell where processes of one kind are in excess over the other a reaction arises which renders the biogen more resistant to further change of the same character, and favors a tendency in the other direction. If, for instance, anabolic changes have been called out in a cell by a stimulus, they generate in time an acceleration of katabolic processes until the two are in equilibrium. The general condition of the cell, however, is *above par*, and is called *allonomous equilibrium*.

When the stimulus is removed, anabolic processes are lessened, and therefore increased katabolism now decreases also; but katabolism, although decreasing, is in excess, and its reaction tends to increase anabolic processes until both are in equilibrium. There is thus an *internal self-adjustment of metabolism* in living matter. It must be borne in mind that metabolism is probably not limited to the building up and breaking down of the biogen, but may be brought about in other substances under the influence of living matter. Such changes are designated *contact changes.*

In order that metabolism may continue, living matter must have a sufficient supply of such material as it can build into its structure. These materials are called *foods,* and may be defined as substances which, taken into the cell, aid in the repair or in the formation of new biogens, adding to the sum total of energy which the cell may liberate, and are finally cast off by the cell in altered chemical condition. The taking in of food by an organism is termed *ingestion.* In very few cases is the ingestion of solid foods possible, so that in order that they may be made use of they are *digested—i. e.,* they are acted upon by complex nitrogenous bodies known as *ferments* or *enzymes,* which convert them into soluble forms. Enzymes are the products of animals and plants possessing the power of producing chemical changes in other bodies without apparently undergoing any change themselves. As the conversion takes place within or without the protoplasm it is designated as *intra-* or *extracellular digestion.*

The steps through which dead matter passes in its synthesis to living matter are very incompletely known. In green plants which thrive on the inorganic compounds, carbon dioxide, water, and simple nitrogenous salts, the first step is observable in the cells of the leaf, where, under the influence of chlorophyll and the energy of the sun's rays (yellow chiefly), the carbon dioxide of the air is split into its elements and the carbon is united with hydrogen and oxygen in the proportions of water to form starch $(C_6H_{10}O_5)_n$. The latter is visible, microscopically, as minute granules, and its formation has been proved to go hand-in-hand with the disappearance of carbon dioxide. This forms the starting point for the formation of all other bodies in the plant. Reconverted to sugars probably, it disappears

from view, is united with nitrogen, which has been taken into the plant in the form of nitrites and nitrates, and is finally built into the structure of living matter. *The successive steps are not known.* Animals cannot live on inorganic salts, but require their nitrogen in the form of proteins, and in this sense are dependent upon plants for continued existence. In all cells the presence of a nucleus or nuclear matter is indispensable to metabolism, playing a predominant part in intracellular oxidation. This has been proved in such cells as liver and kidney cells and in frogs' red corpuscles.

Cell Growth.—The *formation of new biogens* or *growth* takes place only when nuclear matter is normally present, and continues until the cell has reached its maximum size. At this stage the extent of surface of the cell determining the quantity of nutriment that can be absorbed is insufficient to supply the mass of living matter. Such a point is always reached, sooner or later, because, as the cell grows, the surface increases only as the *square* while the volume increases as the *cube* of their like dimensions. Reproduction now takes place, which has appropriately been termed " *discontinuous growth.*" It is always essentially a separation from the body of an individual of a portion of its own material, which under proper conditions grows into an adult organism. In man *growth* continues from the segmentation of the ovum to about the age of twenty-five, and is increased by systematic exercise. It consists not only of an enlargement and multiplication of cells, but of a deposition also of intercellular material. It may be divided into an *embryonic period*, a *fetal period*, *infancy*, *childhood*, *youth*, *maturity*, and *old age*. As growth progresses, the capacity for more growth lessens.

The Origin of Life.—It may be said that as long as the earth was a molten mass of excessively high temperature life could not have existed as we know it today. During the evolution of the earth living matter must have arisen as the result of physical and chemical factors, as all chemical compounds whatsoever have arisen. The formation of living matter was as necessarily the product of evolution as was the formation of water. At first it was probably capable of manifesting vital phenomena indefinitely, which, as a matter of fact, is true of germ cells at the present time. Under proper circum-

stances by means of germ-plasm, life is passed from individual to individual, and in this sense cannot be said to suffer death.

Cell Death.—According to Weismann, *death* has been evolved for the good of the species, since in time, through wear and tear, the vitality of aged individuals is lessened and it is to the advantage of the species that such individuals should no longer propagate or even exist. The term death has, however, many shades of meaning. In one sense living matter is continually undergoing katabolic changes. It is continually dying. The term may be applied to the whole organism or to individual tissues. The first occurs when one or more functions of the body are so disturbed that harmonious action of all the functions becomes impossible.

Somatic Death.—The most convenient sign of somatic death is the cessation of the heart beat, which, however, is not always the cause of death. The *death of the tissues* does not necessarily take place with somatic death. The nervous system dies very soon; the heart lasts longer, the last portion to beat being the right auricle. The smooth muscle of the intestines remains irritable for three-quarters of an hour, and striated muscle at times for hours.

Some of the most important problems of general physiology are as yet highly speculative in character, but most physiologists believe that as knowledge increases they will all, like the phenomena of lifeless bodies, be explained as the result of the properties of matter and energy working under definite laws.

QUESTIONS ON CHAPTER I

Define the term physiology.
What are the principal divisions of physiology?
What is meant by human physiology?
Give the derivation of the term physiology.
When were the earliest physiological ideas formed?
Name some of the earliest physiologists.
What services did Galen, Harvey, Haller, and Müller render?
What is the aim or object of physiology?
How is it possible to tell whether a given piece of matter is alive or not?
What are the fundamental properties of living things?
Define each.
Are they absolutely characteristic of living matter?
What is the "physical basis of life"?
Describe protoplasm.
What is the evidence that protoplasm is a fluid?
What is the finer structure of protoplasm?
Why is protoplasm not a chemical term?
What substance is always present in protoplasm?
What characterizes the elements of living matter?
What is a cell?
What are "histological differentiation" and "physiological division of labor"?
What evidence is there that dead protoplasm differs from living?
Describe the properties of the cyanogen group.
What is a biogen?
What are metabolism, anabolism, and katabolism?
Describe the internal self-adjustment of metabolism.
What is meant by "contact changes" of biogens?
What is the source of the nitrogen of plants?
What is the function of the nucleus in cells?
What can be said of the origin of life?
Give various meanings of the term death.

CHAPTER II

SECRETION

THE term *secretion* may be used to designate either the *liquid* or *semiliquid products* of glandular organs which are discharged upon free or closed surfaces; or to designate the *process* itself by which these products are formed. According as the surface is free (skin, mucous membrane) or closed (blood and lymph cavities) the secretion is termed an *external* or an *internal* secretion. Such substances serving a useful purpose are *typical secretions;* when of no further use, are *excretions.* There is no longer any doubt that *gland cells are active in the formation of their secretions.* The proofs are:

1. The gland cells undergo a microscopic change.

2. Specific substances in the secretion which are not found in the blood or lymph.

3. The liberation of energy in the form of heat, pressure, and electricity.

4. The results of the stimulation of the nerve supply.

5. The action of certain drugs.

The processes of *filtration, diffusion,* and *osmosis* cannot, however, be entirely excluded from acting in conjunction with the physiological properties of the living structure of gland cells. By *filtration* is meant the passage of fluids through a membrane as the result of differences of hydrostatic pressure. *Diffusion* is the interpenetration of the molecules of two fluids when brought into contact. *Osmosis* is the diffusion of water that takes place through membranes separating two solutions.

Salivary Glands.—The production of saliva is brought about by the joint action of three larger pairs of glands, the *parotids, submaxillaries,* and *sublinguals,* and by *innumerable smaller ones* lying in the mucous membrane of the mouth and tongue.

The distinction between *albuminous* and *mucous glands* becomes definite only when applied to individual cells. A series of glands might be gathered, showing every gradation

Fig. 1
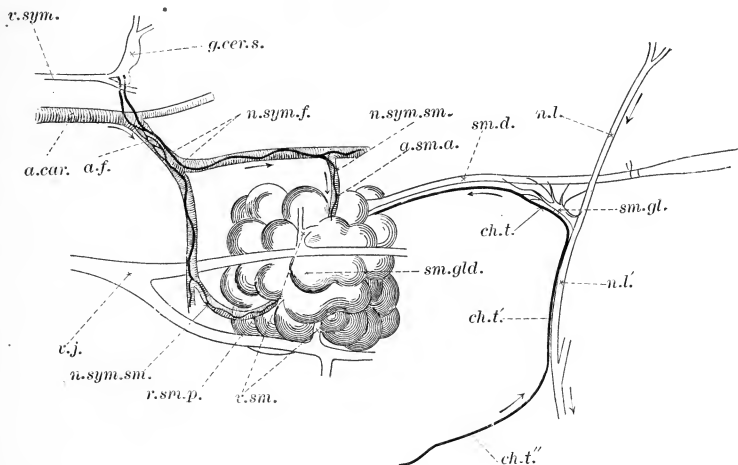
Diagrammatic representation of the submaxillary gland of the dog, with its nerves and bloodvessels. The dissection has been on an animal lying on its back, but since all the parts shown in the figure cannot be seen from any one point of view, the figure does not give the exact anatomical relations of the several structures. (Foster.)

sm.gld., the submaxillary gland, into the duct (*sm.d.*) of which a cannula has been tied; the sublingual gland and duct are not shown; *n.l.*, *n.l.'*, the lingual branch of the fifth nerve; the part *n.l.* is going to the tongue; *ch.t.*, *ch.t.'*, *ch.t.''*, the chorda tympani; the part *ch.t''.* is proceeding from the facial nerve; at *ch.t'.* it becomes conjoined with the lingual *n.l.'*, and afterward diverging, passes as *ch.t.* to the gland along the duct; the continuation of the nerve in company with the lingual *n.l.* is not shown; *sm.gl.*, the submaxillary ganglion with its several roots; *a.car.*, the carotid artery, two small branches of which, *a.sm.a.* and *r.sm.p.*, pass to the anterior and posterior parts of the gland; *v.sm.*, the anterior and posterior veins from the gland, falling into *v.j.*, the jugular vein; *v.sym.*, the conjoined vagus and sympathetic trunks; *g.cer.s.*, the upper cervical ganglion, two branches of which forming a plexus (*a.f.*) over the facial artery, are distributed (*n.sym.sm.*) along the two glandular arteries to the anterior and posterior portions of the gland.

The arrows indicate the direction taken by the nervous impulses during reflex stimulation of the gland. They ascend to the brain by the lingual and descend by the chorda tympani.

from those entirely mucous to those entirely albuminous. The demilunes of Heidenhain in mucous glands are albuminous cells. The two types of cells differ not only histologically, but also in the character of their products. The secretion from albuminous cells contains, besides enzymes, water, salts, and albumin, while that from mucous cells contains mucin, which makes it stringy and viscid.

The *activity of secretory cells* is well shown by the salivary glands. During secretion the granules which are present gradually disappear from the outer side of the cells, and a clear non-stainable material is substituted. The nuclei become more spherical and lie nearer the centre of the cell body, which shrinks in size. The granular material is apparently used up in the formation of the secretion, and since the enzymes formed are specific substances, the former are taken to be their source and designated as *zymogen granules*. The forerunner of *ptyalin* is called *ptyalinogen;* of *pepsin, pepsinogen,* etc.

The *pressure* in the duct of the submaxillary has been observed at 190 mm. Hg, while the blood pressure in the carotid at the time was but 112 mm. Hg. The question of the *amount of heat* given off during the activity of the gland is still unsettled. Ludwig and Spiess originally determined the saliva to be 1° warmer than the blood in the carotid. Heidenhain, by the thermo-electric method, found the difference to become greater on stimulation of the sympathetic. The *electrical* changes in glands are analogous to the action currents in muscles. The current may be ingoing, outgoing, or diphasic in character.

Nervous Factors.—The salivary glands have a *cranial* and a *sympathetic* nerve supply, whose influence may be illustrated by the results obtained from the submaxillary of the dog. When the *chorda tympani,* whose fibers are cranial in origin, is stimulated with weak induction shocks, the saliva obtained is relatively abundant, thin, and watery, containing not more than 1 to 2 per cent. of solids. The gland becomes redder in color, the veins are distended, and the blood shows a distinct pulse, indicating a dilatation of the small arteries and that the chorda tympani carries dilator fibers. Stimulation of the *sympathetic* fibers produces a scanty secretion, which is thick and turbid, and may contain 6 per cent. of solids. The gland

becomes paler, the blood flow is lessened, showing that a vaso-constriction has occurred.

Circulatory Factors.—That the character of the secretion is not entirely due to the changes in the amount of blood flowing to the glands is shown by the following facts:

1. The blood flow may be cut off entirely when stimulation of the chorda tympani still gives a secretion.

2. Injection of atropine produces an increased flow of blood but no secretion, upon stimulation of the chorda.

3. Injection of hydrochlorate of quinine gives a vascular dilatation, but no secretion until the nerve is stimulated.

When the chorda is irritated with shocks of increasing intensity, it is found that the amount of water and salts secreted increases proportionately to a maximum limit, which for salts is about 0.77 per cent., no matter what the condition of the gland may be. The production of organic constituents soon reaches a maximum and then declines, and is closely dependent upon the previous condition of the gland. In order to explain these facts, Heidenhain decided that there were *two sets of nerve fibers*, one of which regulated the formation of organic substances (*trophic fibers*), and the other of which regulated the production of water and salts (*secretory fibers*). Moreover, their arrangement was such that the chorda carried a greater number of secretory, while the sympathetic carried more trophic fibers. Langley has recently offered a simpler explanation of the facts, attributing the differences of the chorda and the sympathetic saliva to the variations in the quantity of blood supplied, so that the assumption of only one kind of secretory nerve fiber is necessary.

Section of the chorda tympani produces after a few days a slow, continuous secretion for five or more weeks, when it ceases. This is called *paralytic secretion*. *Antilytic secretion* is the production of a flow by the corresponding gland on the opposite side, the nerves of which are still intact. *Section of the cervical sympathetic* causes a temporary dilatation of the bloodvessels, but has no other effect. *Atropine* prevents the secretion of saliva by destroying the endings of the cerebral fibers in the gland, leaving, when proper doses are used, the sympathetic fibers still capable of functioning. *Pilocarpine* has an antagonistic action to atropine, causing a continual

secretion by stimulating the cerebral fibers in the gland. *Nicotine* causes a slight flow of saliva, followed by a paralysis. The drug acts upon the end brushes of both the cranial and sympathetic fibers in the superior cervical and submaxillary ganglia.

Mechanism of Saliva Secretion.—The flow of saliva is normally a reflex, the afferent path of which is formed by fibers of the lingual and glossopharyngeal nerves. The centre is said to lie in the medulla near the nuclei of origin of the seventh and ninth nerves. The efferent path for the submaxillary and sublingual glands is along the seventh, the lingual, and chorda tympani nerves. For the parotid the efferent path lies along the ninth cranial, the nerve of Jacobson, the small superficial petrosal, otic ganglion and auriculotemporal branch of the inferior maxillary division of the fifth cranial. Section of these paths prevents the normal reflex in spite of the fact that the sympathetic remains intact. No satisfactory explanation of the functions of the sympathetic secretory fibers has been given.

The reflex mechanism of salivary secretion is very easily set into action. The contact of food with the buccal mucous membrane, the movement of the jaws, or even tasteless objects like India rubber may cause a secretion. The smell, sight, or thought of food may be very effective in making the "mouth water," in which case the result is a so-called *psychical secretion*. Saliva is often reflexly excited through stimulation of the gastric branches of the vagus. Likewise, through stimulation of sensory fibers like the splanchnic or sciatic.

It has been definitely established that a remarkable adaptation exists between the character of the stimulation applied to the mouth and the character of the resulting saliva. When dry food is given to a dog there is poured out an abundant watery saliva; with moist food the flow is much less. Pebbles placed in a dog's mouth are rolled about and finally dropped with but little secretion of saliva. The same pebbles reduced to sand and placed in the dog's mouth give rise to a copious secretion. In the latter case much fluid is obviously necessary to wash the sand out of the dog's mouth. The same adaptive mechanism is found in the varying activity of serous and mucous salivary glands. When fresh meat is given to a

dog hardly any parotid saliva is formed, but the submaxillary, supplying mucin which lubricates the food for swallowing, is very active. When meat is given in the form of a dry powder the parotid is as active as the submaxillary, giving a secretion which is not only abundant but contains mucin. In contrast to this, strong stimulation of the mucous membrane by dis-agreeable, non-edible substances gives rise to an activity of all the glands, but the saliva is poor in mucin, since the substance is not to be swallowed.

In psychical secretion the same adaptation holds good, for it is only necessary to pretend to throw the pebbles or sand into a dog's mouth in order to bring out the same differences in the saliva.

The condition of the salivary centre has an important influence on psychical secretion. A hungry animal responds easily, while in an animal just fed no response is obtainable. Fear or embarrassment or other emotions also affect the salivary centre, inhibiting the normal reflexes. In man the large salivary glands are active intermittently, but the smaller glands are always active.

Gastric Glands.—Two kinds of cells are present in the gastric glands, known as *chief cells* and *border cells*. The former are alone present in the pyloric end of the stomach, and it has been stated by Heidenhain that this portion of the stomach produces no acid. *The pyloric end, carefully resected and converted into a blind pouch, is alkaline in reaction.* This, by exclusion, leaves the border cells as the source of the hydrochloric acid of the gastric juice. During the activity of the gastric glands histological changes take place, especially in the chief cells, similar to those already described in the salivary glands. They also have a double supply of *cranial* and *sympathetic* nerves. Stimulation of the vagi after a latent period of from four and one-half to ten minutes gives a distinct flow. The delay is due to the simultaneous irritation of inhibitory fibers. Stimulation of the sympathetic gives no result.

Mechanism of Gastric Secretion.—In the investigations leading to an understanding of the manner in which the gastric juice is normally secreted, operative procedures have been most fertile in results. A fistulous opening through the abdominal wall leading into the stomach cavity, or, better still, into

a small artificial stomach formed by resecting a protion of the stomach wall gives a means of testing the characteristics of the secretion. Numerous trials have indicated that the secretion of such a small stomach is identical in its properties with the secretion in the main portion of the stomach.

The smell, taste, or sight of food by a dog thus operated upon leads in five or six minutes to the appearance of a copious. secretion. If, furthermore, the esophagus be sectioned in the neck and the cut ends brought to the skin on the neck, a dog may be fed for an indefinite time leading to continued secretion. This "sham" feeding is ineffective if the vagi are cut. In the case of the stomach glands there exists, therefore, a psychical secretion just as in the case of the salivary glands. This has been observed in a human being in which there was an occlusion of the esophagus. It must not be imagined that in sham feeding it is the stimulation of the buccal nerves that reflexly leads to the secretion of the gastric juice. A strong chemical stimulus like dilute acid applied to the mucous membrane of the mouth does not cause a gastric secretion, although the salivary flow is profuse. *It is the appetite that determines the flow of the gastric juice.*

When foods are introduced into the stomachs of sleeping dogs through fistulous openings the effect upon secretion varies with the kind of food. Bread and the white of egg are entirely ineffective during the first hour or so. Raw flesh is more effective, causing a secretion in fifteen to forty-five minutes. Section of the vagi or destruction of the abdominal sympathetic plexus does not abolish the result, especially, after water or meat extract. This difference in results with different foods has given rise to the conception of definite chemical excitants or secretogogues which stimulate the gastric gland cells after absorption. Raw flesh contains them preformed. They are formed in bread and in the white of egg by the action of the psychical secretion. However, food substances (broth, dextrin), containing secretogogues do not stimulate the gastric glands when injected into the blood directly, but must first act on the gastric mucous membrane. The secretogogues are regarded as giving rise to a new substance by their action on the gastric mucosa—a substance known as *gastrin*, representative of that class of substances

known as "*hormones.*" Gastrin is absorbed and carried by the blood to the gastric gland cells, thus exciting them to the formation of their secretory product.

To a certain extent the character of the secretion, as, for instance, in acidity and digestive power, depends upon the character of the food, but this effect is not a specific reaction. For the quantity of the psychical secretion may in the first instance depend upon the relish with which the animal eats the food. The psychical secretion acting upon different kinds of foods may liberate different products, which, determining the quantity of the gastric hormone formed will determine the amount of the secondary secretion.

Pancreas.—The cells of the pancreas are mainly of the albuminous type, in addition to which irregular masses of cells (bodies of Langerhans) are to be found. The latter are clear and small, with readily stainable nuclei. The others show a granular, well-defined, non-stainable zone toward the lumen. During activity the cell boundaries become more distinct and the granular zone becomes narrower. Stimulation of the medulla increases the flow of the pancreatic juice and changes its organic constituents, so that a centre in the medulla is surmised. The nerve fibers supplying the pancreas are comparable to those of the salivary glands in that they are of two varieties—bulbar autonomics and sympathetic autonomics. The former run in the vagus, stimulation of which, however, often fails to produce a secretion, since the pancreas is very sensitive to changes in its blood supply. Changes in blood supply are due to the fact that the tenth nerve contains vasoconstrictors and cardio-inhibitory fibers. This experimental difficulty is overcome by cutting the vagus three or four days previously and then using slow stimulations of one per second. A secretion then follows because the secretory fibers respond to the stimulus while the cardio-inhibitory fibers have degenerated and the vasoconstrictor fibers are not affected by this kind of a stimulus. Having established a pancreatic fistula, it may be seen that the secretion appears in two or three minutes and continues for some time after cessation of the stimulus.

The presence of inhibitory fibers to the pancreas can be established with ease. They exist both in the vagi and sympa-

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thetic nerve supply. Those in the tenth nerve are revealed if this nerve is stimulated while the pancreas is active, for the flow then ceases. Stimulation of the central end of the vagus and of other nerves reflexly inhibits the pancreatic flow. So do painful impressions. Inhibition during vomiting is due to the vagus. It has been maintained that a psychical secretion exists, but this is doubtful, since the results brought forward to prove this can be interpreted as due to the passage of acid chyme into the duodenum.

Mechanism of Pancreatic Secretion.—Pancreatic juice begins to flow in two to three minutes after 0.4 per cent. hydrochloric acid is put into the duodenum. The effect becomes less pronounced in passing along the intestine and is absent in the ileum. This experiment gives positive results from an isolated loop of the intestine, all nerves to which have been cut, the solar plexus extirpated, and after the administration of atropine. The effect, therefore, takes place through the blood, but it is not obtainable by directly injecting the acid into the animal's blood. An extract of the mucous membrane of the duodenum, made with 0.4 per cent. hydrochloric acid, neutralized, and then injected, is effective. The conclusion which is to be drawn, therefore, is that the hydrochloric acid acting on the mucous membrane gives rise to a new body which after absorption into the blood is carried to the pancreatic cells and acts as the effective stimulus. This substance is called *secretin*. It is a diffusible body of low molecular weight, soluble in alcohol or in alcohol plus ether. It withstands boiling and digestion, and is, therefore, not a protein. It is also an effective stimulus to bile secretion, but to no other glands. An extract of the mucosa with 0.7 per cent. sodium chloride gives prosecretin, which does not excite the pancreas, but which can be changed to secretin by boiling or by adding hydrochloric acid. Secretin is widespread and interchangeable between different animals. Since, normally, hydrochloric acid is supplied by the chyme the normal mechanism of pancreatic secretion is through the formation of secretin.

The pancreatic secretion is said to vary in character with the nature of the food. On a bread diet it is poor; on a flesh diet, richer; and on a milk diet, richest in fat-splitting ferment. Bread gives a secretion rich in amylolytic ferment. When

quantity of juice and digestive strength are considered together a bread diet causes a secretion of greater proteolytic power than milk or meat. But there is no more evidence that the adaptation of the pancreatic juice to the nature of the food is due to a specific sensibility of the duodenal mucosa to the various foodstuffs than in the case of the gastric juice. For the volume of the chyme and its acidity determine the amount of secretin formed, and, therefore, the intensity of pancreatic secretion.

It has been discovered that the pancreatic juice obtained from a fistula may have little or no digestive action on proteins unless brought in contact with the duodenal mucosa. The trypsin is secreted in a zymogen form and requires to be activated by a substance furnished by the mucosa. This substance is supposed to be an enzyme, and is known as *enterokinase*. Its action is not specific, since the salts of calcium and magnesium can activate trypsinogen. This relation possibly serves to protect the ducts of the pancreas from digestion.

Internal Secretion of Pancreas.—The pancreas is indispensable to life, especially in carnivora. Loss of the external secretion affects fat digestion, but does not necessarily shorten life. Extirpation of the pancreas, however, in dogs within twenty-four hours leads to profound disturbances in metabolism, showing itself mainly by the presence of sugar in the blood and urine, by polyuria, polydipsia, polyphagia, and emaciation. Dogs may live two or three weeks. Resistance to bacterial invasion is lessened, so that extensive suppuration of the wound often results. When carbohydrates are excluded from the diet, or no food whatsoever is given, sugar still continues to be formed. Protein destruction is increased. When one-fourth to one-fifth of the pancreas is left, even when transplanted (with intact circulation) to other portions of the body, the symptoms are absent. In some manner the pancreas influences metabolism. Since injection of the blood of depancreatized animals into normal animals gives no serious effects, it cannot be that the symptoms of pancreas extirpation are due to the accumulation of toxic bodies within the blood. It is better to assume that the pancreas furnishes the body with something necessary to the regulation of its sugar, either in its storage, or its conversion from glycogen, or its combustion by the tissues.

It is stated that the juices expressed from muscle and pancreas have very little glycolytic power when taken separately, but when combined cause a marked disappearance of sugar added to the mixture. It is assumed that the pancreas furnishes an internal secretion necessary to the consumption of sugar by the tissues. Since the effect is not lost by boiling the extracts, the essential body cannot be an enzyme, but is of the nature of hormones. It is said to be formed by the islands of Langerhans. Injection of paraffin into the ducts of the pancreas gives an atrophy of the ordinary secretion cells only. If a portion of the gland is separated off from the rest and its duct is tied, it undergoes atrophy, leaving only islands of Langerhans and the remains of ducts. If the normal part of the gland is now removed, no glycosuria results, even when dextrose is injected. But a further step in the removal of the atrophied portion gives a typical glycosuria.

There are observers who do not believe that islet tissue differs essentially from the alveolar tissue, and who assert that during exhaustion of the gland a great part of the alveoli is transformed into islet tissue and restored after rest. Lesions of the pancreas are certainly often found in diabetes, and in certain cases the changes observed were in the islands. In cirrhosis of the liver it has frequently been shown that the pancreas also is affected by the growth of connective tissue.

Liver.—The liver possesses three well-recognized functions: (1) It manufactures the product bile, which is partly an excretion and partly a secretion. (2) It is the seat of manufacture of urea, which is passed to the blood and thus to the kidney to be excreted. (3) It forms a prominent storehouse for glycogen.

The amount of bile secreted varies, but for man may be stated to be about 800 c.c. a day. The liver cells which are in relation to the mixed blood of the portal vein and the arterial blood of the hepatic artery are probably *continuously active*. The bile, stored in the gall-bladder, is ejected intermittently. It has been shown that the quantity of bile formed varies with the quantity and quality of the blood supplied to the liver. Bile salts stimulate liver cells, and all such substances are designated as *cholagogues*.

Stimulation of the spinal cord diminishes the secretion,

owing to constriction of the bloodvessels of the abdominal organs. Section of the cord resulting in loss of vascular tone and general fall of blood pressure and velocity decreases the secretion. Stimulation of the splanchnics which have been cut diminishes secretion, owing to vascular constriction of the abdominal organs, while sectioning alone increases the secretion, since the resulting loss of vascular tone is limited to the abdomen, resulting in a greater flow of blood to that region. The determination of distinct secretory fibers for the formation of bile has so far been impossible.

A more important stimulus to bile secretion is secretin. The activity of the liver parallels that of the pancreas, so that it too manifests a definite relation to the digestion of food. This depends upon the amount of chyme passed into the duodenum, for in this way is determined the amount of secretin formed and the time of its formation. In the case of fats a further adaptation follows from the absorption of bile salts, which accompanies the absorption of fatty acids and soaps formed during fat digestion.

The pressure under which bile is secreted is at the most 25 mm. Hg, so that but a slight obstruction, an inflammation of the bile duct or a biliary calculus, leads readily to jaundice.

Formation of Urea by the Liver.—Urea, which is the main end product of protein metabolism, is formed, in part, at least, not in the kidney which excretes it, but in the liver. If an isolated liver is perfused with blood taken from a recently fed dog, the urea contained in it is increased. This is not the case when the blood from a fasting animal is used. The blood, therefore, after digestion contains something that can be converted to urea. Ammonium carbonate is promptly converted to urea if added to the perfusing blood. If the liver is separated from the circulation by the establishment of an Eck fistula, there follows a diminution in the amount of urea in the urine and an increase in the ammonia compounds. It has been shown that the portal vein possesses three or four times as high an ammonia content as arterial blood. Presumably ammonia compounds of the portal blood are converted to urea in passing through the liver.

Glycogen Storage by the Liver.—Glycogen has the general formula of vegetable starch $(C_6H_{10}O_5)_n$. With iodine it gives

a port-wine red color instead of the blue of an ordinary starch reaction. It can in this way be detected in the liver, microscopically. The average amount varies between 1.5 to 4 per cent. of the weight of the liver. In man it forms about 10 per cent. This amount can be increased by feeding, especially if carbohydrates are given in excess. The bulk of man's carbohydrate food is converted into dextrose and levulose, and these when they reach the liver are changed to glycogen and stored. From time to time the glycogen is reconverted to dextrose and given off to the blood, so that the normal sugar content 0.1 to 0.2 per cent. is maintained. The way in which this conversion is brought about is probably through an enzyme, since a diastatic enzyme that changes glycogen to dextrose can be extracted from the liver. Ptyalin converts glycogen to maltose and dextrins.

Intestinal Glands.—It is stated that many cells of the intestinal glands undergo histological changes during activity, in that their granules disappear. *Section of intestinal nerves* leads to an accumulation of fluid in the intestine; but if the *inferior ganglion of the solar plexus is left intact,* the accumulation does not take place.

When a portion of the small intestine is separated into three contiguous compartments by ligatures and the nerves passing to the middle compartment are cut, it can be observed that a secretion, a genuine *succus entericus,* forms in the middle compartment. The secretion may begin in four hours, increase for twelve, and then rapidly diminish so that after two days the compartment is empty like its neighbors. This is looked upon as a paralytic secretion. Mechanical stimulation of the intestinal mucosa gives rise to a local secretion which is an adaptation to the slow movement of the food through the intestine. Such a secretion is poor in enterokinase, but if pancreatic juice be added, the succus entericus becomes rich in enterokinase.

Serous Secretions.—These are produced by the pleura, peritoneum, tunica vaginalis, and by the synovial membranes of joints, tendon sheaths, etc. The *synovial* secretion is more glairy and viscid than a truly serous secretion, which is very much like lymph. The function of serous secretion is to prevent friction between surfaces that are in contact. It is of a pale

yellow color, alkaline in reaction, viscid, and coagulable by heat.

Lacrymal Glands.—The conclusion reached for the salivary glands may be applied with little alteration to the glands of the nasal mucous membrane and to the lacrymal glands. The latter resemble an albuminous salivary gland, receiving *cranial* secretory fibers by way of the fifth nerve, and *sympathetic* fibers by way of the cervical sympathetic. Stimulation of most sensory nerves produces a secretion reflexly. The ducts of the gland lead to the conjunctiva of the upper eyelid, and usually the secretion is just sufficient to keep the eye moist, and is drained into the nasal cavity by way of the lacrymal duct. When the secretion is formed in superabundance, it appears as *tears*. These are alkaline in reaction and contain 1 per cent. of solids, chiefly chloride of sodium.

Secretions of the Skin.—**Perspiration.**—The perspiration is a colorless liquid with a peculiar odor, a salty taste, an acid reaction, and a specific gravity of 1004. The amount formed varies enormously with the temperature, with exercise, with psychical and pathological conditions, but may be put at an average of from 700 to 900 grams a day, a little more than half the total of urine excreted. *Its constituents* are *water, inorganic salts, traces of fat, fatty acids, cholesterin,* and *urea.* Sodium chloride forms from 2 to 3.5 parts in a thousand. The urea of perspiration in determinations of destroyed proteins is usually neglected. During extraordinary muscular work the nitrogen eliminated by the skin amounts to 0.7 or 0.8 gram. Sweat glands are found over the entire surface of the skin, with the exception of the external ear. Their total number is about 2,000,000.

Insensible perspiration increases in quantity with increase of temperature until a certain critical point is reached, when it is markedly increased and appears as *visible sweat*. The percentage of carbon dioxide is increased at the same time. Normally the glands are stimulated by exercise and high temperature. In the latter case it is produced through the central nervous system. Instead of acting on the glands directly, the heat affects cutaneous sensory nerves and reflexly excites the glands. Sweating can be brought about by stimulation of the afferent nerves and by dyspnea; by the latter,

even if the cervical cord is sectioned. Sweat centres are, therefore, surmised in the cord as well as in the medulla, but they have not been definitely demonstrated.

Sebaceous Secretion.—This is an oily, semiliquid material, which sets on exposure to air, and consists of *water, salts, albumin, cholesterin, fats,* and *fatty acids.* Its function is to keep the hair oiled, and perhaps to prevent too great a loss of water through the skin, and also too great an absorption. The sebaceous glands are usually found in connection with hairs all over the body, but on the prepuce, glans penis, and lips they occur separately. The secretion of the prepuce is known as *smegma preputii;* that of the external auditory canal as *cerumen;* that of the skin of the newly born as *vernix caseosa.* In the formation of the secretion the gland cells break down bodily and are replaced by new cells from the layer nearest the basement membrane.

Mammary Glands.—The secretion of the mammary glands is an alkaline, bluish-white fluid, having a specific gravity of 1030. It is a typical emulsion, consisting of a fluid plasma holding suspended fat globules. When the secretion takes place from a newly active gland there are, besides the fat globules, certain albuminous bodies known as *colostrum corpuscles,* which may be cells of the gland or may, perhaps, have their origin in wandering connective-tissue corpuscles. The plasma of the milk consists of water holding in solution casein, lactoalbumin, lactoglobulin, lactose, salts, traces of urea, creatin, and creatinin. The fat globules consist chiefly of stearin, palmitin, and olein, which upon standing rise to the surface as *cream.* Their number in 1 c.c. of milk has been estimated to be from 1,000,000 to 6,000,000. They are not, as was formerly believed, surrounded by an albuminous envelope. Through their high refractive power they are chiefly responsible for the color of milk. The casein which is held in solution by calcium phosphate is, however, partly the cause of the color of milk.

The *reaction of milk* is often amphoteric, and may, especially in carnivora, be acid. Fresh milk is not coagulated by heat, but upon standing it slowly becomes acid through the formation of lactic acid by fermentation, and will then curdle if heated. The *scum* forming on cooked milk is a combination

of casein and calcium. As it is often necessary in infant feeding to replace the mother's by cow's milk, it is important to consider some of the differences between various milks. The following table is modified from König:

Milk.	Specific gravity.	Water.	Casein.	Albumin and globulin.	Fat.	Lactose	Ash.
Woman	1.027	87.41	1.03	1.26	3.78	6.21	0.31
Cow	1.031	87.17	3.02	0.53	3.69	4.88	0.71
Colostrum of cow .	.....	74.67	4.04	13.60	3.59	2.67	1.56
Goat	.....	85.71	3.20	1.09	4.78	4.46	0.76
Sheep	1.034	80.82	4.79	1.55	6.86	4.91	0.89
Mare	1.034	90.78	1.24	0.75	1.21	5.67	0.35
Ass	.....	89.64	0.67	1.55	1.64	5.99	0.51
Hog	.....	84.04	....	.....	4.55	3.13	1.05

The *composition of human milk* varies with the constitution, with the state of nutrition, with age, with the complexion, at different stages of lactation, from the two breasts, etc. It is distinguished from *cow's milk* mainly by the low percentage of protein and the high percentage of sugar. The difference in the protein causes human milk to form a more flocculent and more easily digested precipitate when coagulated. Practically all the phosphorus is in organic combination as nucleon and caseinogen, and is not, as in cow's milk, found as pseudonuclein. The casein in woman's milk is more difficult to precipitate by acids, salts, and rennet, and is also more easily redissolved by an excess of acid.

Human milk contains the fatty acids—oleic, stearic, palmitic, butyric, caproic, capric, and myristic, combined with glycerin. Cow's milk contains, in addition, caprylic and arachic acids. Human milk is poor in volatile acids. The chief base is potassium, while that of other animals is calcium.

The cells of the mammary glands, which during pregnancy become active for the first time, undergo histological changes of such a nature that each cell increases in size, undergoes a fatty metamorphosis, the nuclei divide, and then a portion, at least, of the cell, if not the whole of it, disintegrates. The fragments form the constituents of the milk. There are known instances where the secretion of milk has been suppressed by

strong emotions, epileptic attacks, etc., indicating a control of the central nervous system. The connection between the gland and the uterus, which stand in close relation, is mainly through the blood.

That the secretion of milk may be continuous is not known with certainty, but it is probable that as it accumulates in the sacculated ducts of the gland the tension finally inhibits further secretion. The emptying of the ducts is the normal stimulus, either directly or reflexly, for a renewed activity of the gland. Otherwise the cells undergo retrogressive changes, but they never become as they were before the first pregnancy.

Thyroid Gland.—The thyroid is more or less closely associated with four bodies, the parathyroids, which are totally different in structure and in function. Many of the experimental discrepancies in the past were probably due to failure to recognize this difference. In man the custom of removing the thyroid in cases of goitre often led to unconscious extirpation of all or some of the parathyroids, leading respectively to rapid death or to a condition called cachexia strumipriva. In the latter case the symptoms resemble those of myxedema, and are characterized by hyperplasia. The newly formed connective tissue contains much mucin. The skin is dry and the hair falls out. The expression becomes stupid; there is a decided failure in mental power; and the movements are clumsy and tremulous. When the thyroids are affected early in life a peculiar condition of idiocy, known as cretinism, results.

The symptoms of pure thyroidectomy differ in different animals, being more severe in the young, and more severe in carnivora than in herbivora. Emaciation, muscular weakness, and subnormal temperature are marked. All of these symptoms are obviated if a portion of the thyroid is left in place, or if a portion be grafted into the abdominal cavity or under the skin. Administration of extracts of the gland or even feeding the fresh gland has a similar effect. The active principle in producing this effect is supposed to be a compound rich in iodine, called iodothyrin. The amount of iodine in the thyroid is variable. It is absolutely essential to the normal activity of the gland. The physiological and therapeutic activity of thyroid substance varies directly with the iodine in organic combination.

It has been much debated whether the thyroids form an internal secretion which is necessary to the organism or whether they destroy toxic substances formed elsewhere in the body. In favor of the latter view is the fact that after thyroidectomy the organism cannot cope so readily with poisons introduced from without. There is no evidence that an actual destruction of toxic substances takes place in the gland itself. A far more probable view of the thyroid function is that its secretion is indispensable to the maintenance of the normal level of nutrition, especially of the central nervous system.

It is likely that the secretion of the thyroid is under the influence of nerves, for section of the superior and inferior thyroid nerves is followed by degenerative changes in the gland.

Parathyroids.—Parathyroidectomy after a series of acute symptoms ends fatally within ten days. The symptoms are those of tetany. Tremors, increasing in severity, end in spasmodic attacks and in general convulsions. The pulse rate and respirations are markedly increased; profuse salivation and fever exist. The administration of calcium completely relieves these symptoms and in some animals death may, perhaps, be indefinitely postponed. The tetany produced by ammonia compounds is precisely like that of parathyroidectomy, and it has been shown that the percentage of ammonia in the blood is the same in both cases.

Suprarenal Capsules.—The extirpation of the adrenals in animals leads to a rapid death. Their disease in man, known as Addison's disease, manifests itself in loss of vascular tone, anemia, muscular weakness, and bronzing of the skin. Experimentally it has been shown that intravenous injection of extracts into animals brings about a rapid rise of blood pressure, owing to a constriction of the arterioles and to a strengthening of the heart beat. The heart beats more slowly, however, on account of a reflex inhibition through the vagi. If these are cut the blood pressure rises to enormous heights, possibly to four or five times the original height. There is reason to believe that the active principle of such extracts, adrenalin, also affects the vasomotor centre. It is said to exert its action mainly on structures supplied by sympathetic nerve fibers. The effect is still more pronounced when the nerve fibers have

degenerated so that it is assumed that a special receptive substance exists at the myoneural junction. Smooth muscle which has not been in connection with sympathetic nerve fibers is unaffected. Thus, adrenalin causes a diminution of tone of the small intestine and stomach and a disappearance of peristalsis. Inhibition of the contractions of the urinary bladder and gall-bladder; contractions of the uterus, vas deferens, and seminal vesicles; dilatation of the pupil, stimulation of the salivary and lacrymal apparatus are likewise caused.

Adrenalin ($C_9H_{13}NO_3$) is to be found only in the medulla of the suprarenal capsules. The cortex, as far as is known, has a very different function. It is said to contain cholin, which lowers blood pressure, and the attractive theory has been suggested that in this way the suprarenal capsules exert a double chemical control upon the circulation comparable to the double nervous control. The existence of secretory nerves to the suprarenal capsules has been made probable by the increase of active substance in the suprarenal vein following stimulation of the splanchnics.

The amount of adrenalin necessary to produce a physiological effect is extremely small. One-millionth of a gram per kilo of body weight is sufficient to cause a distinct rise in blood pressure. The action is but a temporary one, owing to a rapid oxidation of the adrenalin.

The active substance of the suprarenal capsules is furnished by the so-called *chromaffin* cells which make up the medulla and stain brown with chromic acid or chromates. An artificial adrenalin has been synthetically prepared. Although chemically, like the natural substance, it is optically inactive, while the other turns the plane of polarization to the left. The synthetic product is said to consist of equal parts of levorotatory and dextrorotatory adrenalin. The artificial adrenalin has only one-half the effect of the natural on blood pressure, so that it is inferred that the dextrorotatory isomer has practically no pressor effect. When these two isomers are separated the left rotatory has the same pressor effect as natural adrenalin, while the other, the right rotatory, has only one-twelfth to one-fifteenth as much power. Adrenalin has the power of producing glycosuria when injected. Repeated injections lead to tolerance.

Pituitary Body.—When this body is completely removed from dogs death results in from one to two days. Although the animal may make good recovery from the immediate effects of the operation, it soon becomes comatose, with long-drawn inspirations, feeble pulse, limp muscles, subnormal temperature, and with characteristically curved spine. Death ensues quietly. Partial removal of anterior or posterior lobes gives rise to no disorder, but complete removal of the anterior lobe alone gives the same results as total extirpation of the gland.

The pituitary is said to hypertrophy after thyroidectomy, and the colloid formed by the pars intermedia is said to be increased and to invade the pars nervosa of the gland. This colloid, however, seems to contain no iodine. In man, pathological changes of the pituitary are not associated with myxedema, but with acromegaly, a condition in which the bones of the limbs and face, especially of the lower jaw, become enlarged. Whether this is due to a hypo- or a hypersecretion is not known.

All three parts of the pituitary contain a substance which when injected into an animal produces a depressor effect. But since this is an effect of so many extracts of tissues, especially nervous tissues, it is not regarded as specific to the pituitary. The posterior lobe including the pars intermedia contain, in addition, an active substance producing a pressor effect. This is produced not only by a constriction of the arterioles, but by an increase of heart beat. The rise of pressure lasts a long while, and a second dose injected before the effects of the first have passed off is without further effect, thus distinguishing the pituitary from the suprarenal.

Spleen.—The function of this organ is very little understood. It may be removed from the organism without serious injury, giving rise, it is asserted, to an enlargement of lymph glands and to an increase in the amount of bone marrow. It has also been found that the number of red blood corpuscles is diminished. The following suggestions of the function of the spleen have been offered:

1. That the spleen manufactures blood corpuscles. This is without doubt true in man during fetal life and at birth, but it is not known that it continues throughout life.

2. That the spleen destroys the red blood corpuscles. The evidence for this theory is that spleen tissue is rich in iron-holding compounds, and that certain ameboid cells of the spleen have been seen apparently ingesting and destroying red blood cells.

3. That the spleen produces uric acid. Uric acid is found in the spleen, but also in all lymphoid tissue.

4. That the spleen produces an enzyme which is carried to the pancreas in the blood, converting trypsinogen into trypsin. A striking feature of the spleen is its *rhythmic movements*. It undergoes a slow expansion and relaxation, with definite periods of digestion. These are due to vasomotor changes, the maximum vasodilatation occurring about the fifth hour after a meal. In cats and dogs there are, in addition, rhythmical changes taking place from minute to minute which serve to maintain a constant circulation through the organ. The spleen is well supplied with nerves, stimulation of which produce a contraction.

The *chemical substances* found in the spleen are interesting, since they indicate a marked metabolism. There is a large percentage of iron in an unknown organic combination. In addition, there are fatty acids, fats, cholesterin, xanthin, hypoxanthin, adenin, guanin, and uric acid.

Thymus.—There seems to exist a reciprocal influence between the thymus and the sexual glands. The thymus persists longer than normal in castrated animals, and premature removal of the thymus is followed by a rapid growth of the testes. In young mammals the removal of the thymus causes a transient disturbance in nutrition; a temporary decrease in the number of leukocytes and a diminished resistance to pus-forming organisms.

Ovary and Testis.—In addition to the prime function of the sexual organs as organs of reproduction there is much evidence that they influence the processes of growth, partly, at least, through the production of an internal secretion. During the breeding season the muscles of the forearm of Rana fusca become hypertrophied in order to hold the female more firmly. At the same time the balls of the toes increase in size and become covered with a black growth. In castrated frogs these events do not occur, but they return if a piece of testicle

from a normal frog is introduced under the skin of the castrated frog. In castrated bitches it has been shown that there is a distinct specific lessening of metabolism, with lessened oxygen consumption. Administration of ovarian extract (*oöphorin*) increases the gaseous exchanges above the original amount, but has no effect upon a normal uncastrated animal.

Brown-Séquard first investigated the internal secretion of the testis. He showed that an extract of the gland or of the spermatic fluid when injected under the skin will produce mental and physical vigor in cases of prostration, neurasthenia, and old age. The active substance has been isolated and called *spermin* $(C_5H_{14}N_2)$. It is not essential to life, since the testes may be removed without fatal results. It is a well-known fact that ovariotomy and premature menopause may be followed by abnormal mental symptoms and often by a gain in weight. In *osteomalacia*, a disease giving rise to a softening of the bones, removal of the ovaries has been found to exert a favorable influence. In dogs complete ovariotomy is followed by a lessening of the consumption of oxygen, which is increased again by feeding with ovarian extracts. These facts show the influence of the ovaries upon the general nutrition.

A temporary diminution of hemoglobin and of erythrocytes in castrated bitches favors the view that insufficient internal secretion of the ovary is the cause of chlorosis. The corpus luteum is the source of an internal secretion that influences menstruation and the implantation of the ovum as well as the subsequent growth of both ovum and uterus.

Kidney.—Although the kidney is richly supplied with nerves, there is no indisputable evidence of secretory fibers, but changes in the secretion of urine can be explained by variations in the blood flow. It has been estimated that the supply of blood to the kidney may be from four to nineteen times as large as that of other organs of the body, and equals per minute 5.6 per cent. of the total quantity sent out by the left heart. The secretion of urine can be measured directly, but variations in blood supply are determined by an instrument called an *oncometer*. A rich supply of vasoconstrictor fibers for the kidney emerge from the cord in the lower thoracic spinal nerves (dog), pass through the sympathetic system, and reach the kidney as non-medullated nerves. Stimulation of

these nerves causes a shrinkage of the organ and a diminution of the secretion. When the fibers are cut, the arteries dilate, the organ enlarges, more blood passes through the kidney, and the secretion is augmented. The vasodilator fibers to the kidney emerge from the cord through the anterior roots of the eleventh, twelfth, and thirteenth spinal nerves. Normally the fibers—*i. e., constrictors* and *dilators*—are brought into activity reflexly and regulate the formation of the secretion. Any factor that increases the difference in pressure in the renal artery and the renal vein will cause increased secretion of urine. Vascular dilatation of the vessels of the kidney, unless counterbalanced by a general fall of blood pressure, will give an increased secretion. The following table is useful for reference:

TABLE OF THE RELATION OF THE SECRETION OF URINE TO ARTERIAL PRESSURE. (KIRKE.)

A. *Secretion of urine may be increased*—
    (a) *By increasing the general blood pressure by*—
        1. Increase of the force or frequency of the heart beats.
        2. Constriction of the small arteries of areas other than that of the kidney.
    (b) *By increasing the local blood pressure by relaxation of the renal artery, without compensating relaxation elsewhere by*—
        1. Division of the renal nerves (causing polyuria).
        2. Division of the renal nerves and stimulation of the cord below the medulla (causing greater polyuria).
        3. Division of the splanchnic nerves; but the polyuria is less than in 1 or 2, as these nerves are distributed to a wider area, and the dilatation of the renal artery is accompanied by dilatation of other vessels, and, therefore, by a somewhat general increase of blood supply.
        4. Puncture of the floor of the fourth ventricle or mechanical irritation of the superior cervical ganglion of the sympathetic, possibly from the production of dilatation of the renal arteries.
B. *Secretion of the urine may be diminished*—
    (a) *By diminishing the general blood pressure by*—
        1. Diminution of the force or frequency of the heart beats.
        2. Dilatation of capillary areas other than that of the kidney.
        3. Division of the spinal cord below the medulla, which causes a dilatation of the general abdominal area, and urine generally ceases being secreted.
    (b) *By increasing the blood pressure* by stimulation of the spinal cord below the medulla, the constriction of the renal artery which follows not being compensated for by the increase of general blood pressure.
    (c) *By constriction of the renal artery* by stimulating the renal or splanchnic nerves or the spinal cord.

Mechanism of Urinary Secretion.—Theories on this subject group themselves, more or less definitely, about two points of view, so that there are physical explanations and physiological explanations. A tremendous amount of ingenuity has been shown in experimentation in attempting to establish one or the other point of view. At present the evidence is most decidedly in favor of the physiological theories, which it must be remembered do not exclude physical factors.

Ludwig regarded the secretion of urine as due to simple filtration and osmosis taking place in the glomeruli, and to a concentration in the convoluted tubules, of the fluid thus formed.

Recent work has shown that the cells of the convoluted tubes have a distinct secretory function in the elimination of urea and related bodies. The evidence is:

1. In birds, where uric acid takes the place of the urea in mammals, the small solubility of the urates enables experimenters, by ligation of the ureters, to cause a deposit which is always found in the cells of the convoluted tubes.

2. Indigo carmine injected into the circulation of a living animal may be precipitated by the injection of alcohol, when the pigment is always found in the convoluted tubes.

3. The inactive cells of the convoluted tubes are small, granular, and toward the lumen show a striated border. During activity they lose their striated border, project into the lumen of the tubule, making it smaller, and a clear vesicular area is formed near the nucleus. The vesicle ruptures and empties its contents into the lumen.

The excretion of water and salts takes place mainly through the glomerular epithelium. There are no secretory nerves. Section of the cord in the cervical region, which results in a general fall of blood pressure, diminishes the secretion. In general it has been found that the secretion of urine varies both with the pressure of the blood in the glomeruli and the quantity of blood flowing through the kidney, and Heidenhain has insisted upon the latter factor as the essential one, giving as evidence the fact that compression of the renal vein stops the flow of the urine. This raises the pressure in the glomerulus, but stops the flow of blood. Ligation of the vein for one-half minute will stop the secretion for three-quarters of an hour,

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so that it probably depends upon the living structure of the epithelial cells.

It is a very instructive condition when in the blood the normal proteins and sugar of the blood circulate side by side with egg albumin, peptone, and cane sugar. The kidney cells then show a selective action, excreting the latter and not the former. Likewise, urea and dextrose, both highly diffusible substances, are simultaneously present in the blood reaching the kidney. Urea is present to the extent of four parts per ten thousand, but there is three times as much sugar. Yet the kidney selects the urea for excretion and rejects the other.

The separation of urine from blood implies the performance of a large amount of work in overcoming differences of osmotic pressure. The osmotic pressure of a liquid is readily determined by noting the depression of the freezing point. Plasma, for instance, freezes at $-0.6°$ C. This is expressed as follows: $\triangle = -0.6°$ C. Likewise, $\triangle$ for urine is equal to $-1.8°$ C. When these values are translated into meters of water pressure it is found that the urine exerts 225 meters of water pressure, while plasma exerts but 75 meters of water pressure. The urine, therefore, considering this factor only, would tend to diffuse back through the kidney cells into the blood with a force equal to 150 meters of water pressure. This would be opposed only by the normal hydrostatic pressure between blood and urine equal to only 1.35 meters of water. The passage of urinary constituents is, therefore, from a region of low to a region of high osmotic pressure.

The quantities of water lost through the kidneys and skin stand in inverse proportion to one another. Since water lost through the skin affects the normal constitution of the urine through the medium of the blood, it is to be expected that other substances in the circulation might have similar influence. This, as a matter of fact, is true. A temporary alteration of the blood by the absorption of large quantities of water and the presence of diuretics increases the flow of water from the kidneys. If *saline diuretics* (potassium nitrate, sodium chloride, urea, dextrose, etc.) are injected into the blood, an abundant secretion soon takes place, which is accompanied by an enlargement of the kidney and a slight rise of blood pressure. It has been shown that the power of these diuretics is propor-

tional to their molecular weights, and it is, therefore, highly probable that through their osmotic power they withdraw water from the tissues to the blood. The diuresis which they bring about lasts only as long as the blood pressure remains above normal.

Other diuretics are *caffeine* and *digitalis*. If one-half grain of caffeine is injected into the circulation the kidney at first contracts in volume and the secretion of water is stopped. Soon, however, an expansion takes place and a copious urinary flow results. The general blood pressure is also lessened and then heightened. Caffeine seems to act on the renal vessels, diminishing and then augmenting the flow of blood through the glomeruli. Digitalis is rather uncertain in its action as a diuretic. It slows and strengthens the beat of the heart in certain subjects, increasing the arterial pressure and lowering the venous pressure, which favors the flow of blood through the kidney and produces an increase in the amount of water in the urine.

Diuretics may be considered as acting in the following ways:

1. They may cause hydremic plethora by drawing water from the tissues, thus increasing the blood pressure and favoring filtration.

2. The substances may act directly upon the cells of the glomeruli.

General anesthetics also affect the activity of the renal epithelium. Ether increases while chloroform decreases the secretion. From this point of view a mixture of ether and chloroform would be the anesthetic to be preferred.

It may be tentatively accepted as most nearly expressing present ideas upon kidney secretion that the water and salts of the urine are chiefly separated by the glomeruli; the process is not a mere physical filtration, but a physiological activity. Physical forces and processes are not excluded, but they act under conditions and produce results in a manner not conceivable under present conditions of knowledge, so that it would be proper to call the activity a vital activity. Substances like sugar, peptone, egg albumin, and hemoglobin when injected into the blood are probably excreted mainly by the glomeruli; and so is the sugar in diabetes. Urea, uric acid, and other constituents of normal urine, with a portion

of the water and the salts, are excreted by the activity of the epithelium of the renal tubules.

QUESTIONS ON CHAPTER II

What is the meaning of the term secretion?
Distinguish between internal and external secretions.
Give proofs that gland cells are active during secretion.   Discuss.
What physical processes are involved in secretion?
What is the source of the saliva?
Distinguish between albuminous and mucous secretions.
Give, in detail, the mechanism of saliva secretion.
What is meant by paralytic and antilytic secretions?
What is the source of the gastric juice?
Give, in detail, the mechanism of gastric secretion.
What is the effect of the stimulation of nerves supplying the pancreas?
Give, in detail, the mechanism of pancreatic secretion.
What is secretin?   Give its properties.
What is enterokinase?
Discuss the relation between the character of the secretion and the nature of the food.
Why does extirpation of the pancreas lead to profound metabolic disturbances?
What evidence is there that the pancreas yields an internal secretion?
In what way are the islands of Langerhans involved?
What are the functions of the liver?
What are the results of the stimulation of nerves on bile secretion?
What is the normal stimulus to bile secretion?
Discuss the formation of urea by the liver.
Discuss the storage of glycogen by the liver.
Is the activity of intestinal glands under nervous control?
What are serous secretions?   Describe properties.
Tell what you can of the lacrymal glands.
What are the secretions of the skin?
What is the composition of perspiration?   How formed?   What relation to insensible perspiration?
Discuss the sebaceous secretion.
Where is milk formed?   Describe milk.
How does human milk differ from cow's milk?
What histological changes occur during milk secretion?
What are the symptoms of thyroid extirpation?
How may these symptoms after extirpation be obviated?
What is iodothyrin?
What is the method of action of the thyroids?
Discuss the function of the parathyroids.
Describe the result of extirpation of the suprarenal capsules.
Describe the result of intravenous injection of extracts of the suprarenal capsules.
Are different kinds of smooth muscle affected in the same way by suprarenal extracts?
What is the source of the adrenalin of the suprarenal capsules?
How do the natural and the artificial adrenalin compare?
What dose of adrenalin is necessary to produce a physiological effect?
What is the effect of extirpation of the pituitary body?
What are the symptoms of disease of the pituitary body?

Discuss the function of the spleen.

Discuss the physiology of the thymus gland.

What are the functions of the ovary and testis?

What is spermin?

What relation exists between chlorosis, menstruation, and the ovaries?

How is the blood supply of the kidney related to its nerve supply?

How may the secretion of urine be increased by varying the blood pressure?

How may the secretion of urine be decreased by varying the blood pressure?

What is the mechanism of urinary secretion?

What are diuretics and how do they act?

CHAPTER III

DIGESTION

An examination of all the various substances that ordinarily serve mankind as food reveals the fact that they consist of one or more simpler components known as *foodstuffs*. These may be defined as materials absolutely necessary to the maintenance of the normal composition of the body; to the growth of new tissue and to the repair of tissue waste; or as materials yielding energy to the body. Futhermore, a food must exert no injurious effect upon the organism. Viewed from this point of view, foodstuffs fall into five or six groups—water, inorganic salts, proteins, albuminoids, carbohydrates, and fats. Oxygen is also absolutely necessary to the maintenance of life, but it is not ordinarily regarded as a foodstuff. In addition to the above there are other substances ingested with food whose value is an indirect one in that they make eating more agreeable. These accessory articles of diet are flavors, condiments, and stimulants.

Foodstuffs.—1. **Water and inorganic salts** are constantly being lost from the body, so that they must be replaced in the food. They serve in maintaining proper osmotic relations between tissue elements, but furthermore, enter most intimately into vital reactions. In the case of salts some of these reactions are undoubtedly ionic effects.

2. **Proteins and Albuminoids.**—Proteins are absolutely essential to the body, since they are the sole available source of nitrogen. They serve for the repair of old tissue, for the formation of new tissue and as a source of energy. They contain the elements carbon, hydrogen, nitrogen, oxygen, sulphur, and sometimes phosphorus and iron. Hundreds of atoms are contained in a molecule; the formula for egg albumin, for instance, has been given as $C_{204}H_{322}N_{52}O_{66}S_2$. When proteins are broken down

by the action of ferments or by boiling with dilute acids the most important of the cleavage products are various *amino-acids*. The different proteins differ quantitatively and qualitatively as regards the number and kinds of *amino acids* liberated. Thus, serum albumin and egg albumin yield no glycocoll, while it is constantly present among the cleavage products of serum-globulin. Leucin is present to the extent of 20.5 per cent. in horse's serum albumin, while egg albumin yields only 7.1 per cent. Gelatin, which yields 16.5 per cent. of glycin, gives no tyrosin or tryptophan at all, while egg albumin and serum albumin yield tyrosin in different amounts. The process by which the protein molecule is decomposed is called hydrolysis. The molecules take up water and split into smaller molecules. This takes place in various stages, bodies like acid-, or alkali-albumin, being first formed, then proteoses, then peptones. The latter are further split into bodies containing a relatively small number of amino-acids linked together. These bodies are called *polypeptids* and are ultimately broken up into individual amino-acids. The synthesis of amino-acids into increasingly complex polypeptids has been accomplished until bodies giving the characteristic reactions of peptones have been obtained.

Carbohydrates.—As regards chemical constitution, the simplest carbohydrates are aldehydes or ketones, *i.e.*, they are the first oxidation products of primary and secondary alcohols respectively. The sugars containing six carbon atoms are termed hexoses. Examples: dextrose, levulose, and galactose. The empirical formula of these three is the same ($C_6H_{12}O_6$), but owing to the different arrangement of the atoms or groups of atoms they have each their own characteristic properties. Dextrose rotates the plane of polarization to the right, levulose to the left. By the union of two molecules of a monosaccharide with loss of a molecule of water, a disaccharide is formed. Examples of the latter are cane sugar, maltose, and lactose, each with the same empirical formula ($C_{12}H_{22}O_{11}$). Cane sugar yields on hydrolysis equal parts of dextrose and levulose; lactose yields dextrose and galactose; while maltose is converted into dextrose. By the condensation of more than two molecules of monosaccharides, polysaccharides are formed, such as starch, dextrin, and glycogen. Their general formula is written ($C_6H_{10}O_5$)$_n$; the value of n may be several hundred.

Fats.—These are compounds of higher fatty acids and glycerin. Ordinary body fat consists of mixtures of three neutral fats (palmatin, stearin, and olein). Olein melts at —0.5° C., while palmatin and stearin melt at temperatures higher than body temperature. Fats are soluble in ether and in hot alcohol, but not in water.

Enzymes.—In passing along the alimentary tract the various foods or foodstuffs undergo a series of physical and chemical changes, which, grouped together, constitute the digestion of food. The effect of these changes is largely the transformation of insoluble, indiffusible substances into simpler, soluble, and diffusible substances. The chemical changes are of a peculiar character and are due to the presence of enzymes in the secretions which are poured into the alimentary tract. Enzymes are bodies of unknown structure whose presence is inferred from the changes which demonstrably take place in the foods undergoing digestion. Their essential nature is unknown. They are not necessarily protein, but many of them give protein reactions. They are non-living bodies, although derived from living bodies. They are believed to be colloids. In some there is present some inorganic substance which is essential to its action. Examples are hydrochloric acid loosely combined in pepsin and manganese in the ferment laccase.

Enzymes are present in the digestive secretions in very small amounts and act with extraordinary energy, without being themselves used up in this process. The old distinction between organized ferments and unorganized ferments, or enzymes, has lost significance since an increasing number of organized ferments have yielded enzymes which do their characteristic work when separated from living cells just as well as when part of the living organism. A better classification is into intracellular and extracellular enzymes, *i. e.,* those enzymes which normally act within or outside of the cells which produce them. The digestive enzymes, on this basis, are mainly extracellular. Taken altogether they exhibit a number of general properties:

(*a*) They are soluble in glycerin and in aqueous or saline solutions. Some act best in alkaline, some in neutral, and some in acid media.

(*b*) From such solutions they are precipitated by an excess of alcohol. Enzymes also tend to adhere to any inert precipitate, and this is a recognized procedure in their isolation and purification.

(*c*) All have an optimum temperature lying somewhere between 37° and 50° C. A rise of temperature to 80° C. kills them.

(*d*) The accumulation of the products of action hinders further action and finally, apparently, stops it. This phenomenon in some enzymes, at least, has been demonstrated to be due to their *reversibility of action.* Lipase, for instance, will not only break ethyl butyrate into ethyl alcohol and butyric acid, but once having formed the latter, reunites them into ethyl butyrate. So complete a reversal of action does not always take place. Maltase acting on maltose will change the latter to dextrose, but when maltase is allowed to act upon a solution of pure dextrose some of the dextrose is converted to isomaltose and dextrin-like bodies.

(*e*) Enzymes often exist in active and inactive forms. The latter, known as zymogen, is often visible in cells in the form of granules. When a ferment is secreted in an inactive form it often requires some second body to produce the conversion into the active form. When this second body happens to be an inorganic substance it is called an *activator;* when, on the other hand, it is an organic substance it is called a *kinase.*

The nature of the chemical change brought about by enzymes is in very many cases, especially in digestive processes, one of hydrolysis. In producing this reaction they are said to act by *catalysis,* which means by their mere presence. It is conceivable that a ferment may act through its physical properties or through certain chemical changes that it undergoes, but which leave it ultimately as it was at the beginning. Both possibilities may be illustrated by phenomena from inorganic nature. For instance, a trace of iodine added to amorphous phosphorus will convert the entire mass into red phosphorus. The iodine undergoes no chemical change, but acts through its physical properties, possibly by inducing a more active molecular vibration in the phosphorus, so that it assumes a more staple structure. Chittenden has given an example illustrating the other possible method of action of enzymes. Carbon

monoxide and oxygen, when perfectly dry, cannot be made to unite by means of an electric spark, but if a small quantity of water vapor is present they combine readily. The following equations explain the reactions. In them it is seen that water takes part in the reaction, but remains finally as it was at the beginning:

$$2H_2O + CO + O_2 = CO(OH)_2 + H_2O_2.$$
$$H_2O_2 + CO = CO(OH)_2.$$
$$2CO(OH)_2 = 2CO_2 + 2H_2O.$$
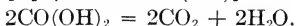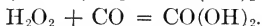
There is much more certainty in regard to the changes produced in the bodies upon which the enzymes have acted. These are in most cases *hydration changes—i. e.*, the substances acted upon take up water and then break down into simpler combinations. The reasons for this belief are as follows:

1. Enzymes act only in the presence of water.

2. In many cases an examination of the substances before and after fermentation show directly a taking up of water.

3. The action of ferments may be imitated by dilute acids or alkalies, which are the most powerful hydrolytic agents known.

Salivary Digestion.—The saliva is a transparent, viscid fluid. It is normally alkaline in reaction. The amount formed in twenty-four hours is about 1500 c.c. When taken from the mouth it is known as *mixed saliva*, and is turbid, owing to suspended particles of matter. It contains characteristic *salivary corpuscles*, which are probably altered leukocytes. Chemically it consists of 99.5 per cent. water, holding in solution salts, proteins, and the ferment *ptyalin*. The viscidity is due to a glycoprotein *mucin*. Saliva keeps the mouth moist in chewing and in speaking, dissolves certain substances, and so brings them in contact with the organs of taste, makes swallowing possible by wetting the food, and acts by means of its ferment on starches. *Ptyalin, by a process of hydration, converts starch to maltose through numerous intermediate steps.* The first change is probably the formation of soluble starch, which, by further action of the enzyme, gives off a molecule of maltose, leaving a body known as *erythrodextrin*. The latter may be detected by the red color it gives upon the addition of iodine. Erythrodextrin, by a further splitting off of a mal-

tose molecule, is converted into a series of *achroödextrins*, which give no color reaction with iodine. These are, by the continued splitting off of maltose molecules, finally all converted into maltose. Ptyalin acts in a neutral or slightly alkaline medium. Free hydrochloric acid to the extent of 0.003 per cent. stops its action, which, taken in connection with the fact that the food remains in the mouth but a very short time, was thought to indicate that the ptyalin digestion is not very important and is limited to the initial stages; but recent progress in knowledge of the conditions in the stomach shows that salivary digestion may continue for an hour or more in the fundic end of the stomach. Cooked starch is more readily acted upon than raw, owing to the fact that the cooking destroys the cellulose envelope that surrounds the starch grains.

Gastric Digestion.—The gastric juice is a thin, nearly colorless liquid, of strong acid reaction and of a peculiar odor. Its specific gravity varies from 1.002 to 1.003. Its constituents are some protein, some mucin, inorganic salts, hydrochloric acid, and the enzymes, pepsin, rennin, and lipase. The acid of the gastric juice is proved to be free hydrochloric acid in the following ways:

(*a*) When all the chlorides are precipitated by silver nitrate and the total chlorine is determined, more is found than can be held by the bases present.

(*b*) The secretion gives the color tests for free mineral acids —methyl violet solutions are turned blue, etc. The amount of free acid varies, but may be put at 0.3 to 0.5 per cent. It has been attempted to determine the source of the hydrochloric acid by injecting into the circulation of an animal substances like ferric lactate, followed by potassium ferrocyanide, which react only in the presence of a free mineral acid with the production of Prussian blue. But this only in a general way proved its formation in the gastric mucous membrane, leaving the method of its formation unrevealed. During the active secretion of the gastric juice the alkalinity of the blood is increased and the acidity of the urine is decreased, corroborating the view that neutral chlorides are decomposed, the chlorine going to form the hydrochloric acid, while the bases pass back into the blood.

Pepsin is a proteolytic enzyme that acts only in acid media. A piece of fibrin, for example, when subjected to an artificial gastric juice swells up and finally passes into solution. It is changed into a more diffusible form of protein called peptone, but this conversion takes place through a number of intermediate steps. There is, first, the formation of an acid albumin, which has been named *syntonin*. Upon neutralization of the medium, syntonin is precipitated, and upon further addition of the alkali is converted into *alkali albumin*, which again passes into solution. Syntonin is by hydrolysis changed to a series of bodies known as *primary proteoses*. These in turn undergo cleavage with the formation of *secondary proteoses* or *deuteroproteoses*. The latter finally become, by the further action of the ferment, *peptones*.

The original protein molecule has undergone a series of hydrolytic cleavages, so that there is obtained a large number of much smaller, more soluble molecules whose molecular weights are perhaps only 250 or so instead of 5000 or 7000, the weight of the original protein molecule. The peptones are a group of compounds which, while still showing the protein (biuret reaction), are not coagulated by heat nor precipitated by saturation with ammonium sulphate. There is evidence that along with peptone, or in place of it, the further action of pepsin gives rise to certain simpler bodies which no longer give the biuret test and are not precipitable by phosphotungstic acid. These apparently are polypeptids. In addition, finally, amino-acids and nitrogenous bases may be found.

Rennin.—The gastric juice contains an enzyme that coagulates milk. The latter, if left undisturbed at the proper temperature, sets into a solid clot, which shrinks and presses out a clear, yellowish liquid called whey. The curd of human milk is not a solid, but is deposited in loose flocculi. Rennin acts upon caseinogen, giving rise to a modification known as paracasein. The latter unites with calcium salts and is precipitated as the curd. If soluble calcium salts are removed from milk by the addition of oxalate solutions it will not curdle under the influence of rennin. Addition of lime salts restores the coagulating power. Casein is precipitated by an excess of acid. This takes place in the souring of milk. Here the bacteria, acting upon milk sugar, produce lactic acid, which,

when the concentration is sufficient, precipitates the casein. The value of the curdling is not at all clear unless it is assumed that under the conditions that exist in the body casein is better digested by being converted to a solid form. Rennin is found elsewhere than in the gastric mucosa. Wherever proteolytic enzymes are found there is evidence of a curdling action on milk, so that some observers have urged the view that milk coagulation is not due to a specific ferment, but is due to the pepsin. The curd formed by the action of rennin has been much more profoundly affected than the precipitate formed by acid. The latter may be redissolved and later curdled by rennin, but a procedure in the reverse direction is not possible.

Lipase.—In the stomach the protein substances which form the envelopes of fat cells and the substances which keep the fat globules of milk apart are dissolved by the pepsin-hydrochloric acid. The freed fats, liquefied by the heat of the body, then run together and, mixed mechanically with other food substances, pass from the stomach as chyme. In addition, a considerable amount of the fat is split up. Gastric juice will produce this result, *in vitro*, in media of either neutral or acid reaction, but is very sensitive to an alkaline reaction. A glycerin extract of the gastric mucous membrane is much more resistant to an alkaline reaction, but is very sensitive to acid. This indicates that the ferment lipase exists in the mucous membrane in a different form from that in which it is secreted. In other words, it exists in a zymogen form.

Digestion in the Small Intestine.—In this portion of the alimentary tract the pancreatic juice, the bile, and the intestinal juice act upon the food, which as a result undergoes here its greatest digestive changes.

The pancreatic secretion is a clear, slightly viscid liquid and of an alkaline reaction, due mainly to sodium carbonate. Its neutralizing power is not much less than that of an equal amount of gastric juice. The solid constituents form about 2 per cent., being chiefly inorganic salts and proteins. The quantity secreted by man, per day, varies from 500 c.c. to 800 c.c. Pancreatic juice contains four ferments: (1) Trypsinogen, the precursor of a proteolytic ferment, trypsin; (2) a starch-splitting ferment, amylopsin; (3) a fat-splitting

ferment, lipase or steapsin; (4) possibly a milk-curdling ferment. The curdling effect may be due to trypsin.

Trypsinogen has no action on proteins until, as a result of the action of enterokinase of the intestinal mucosa, it is changed to active trypsin. Enterokinase activates the trypsinogen. It then acts more energetically than the pepsin-hydrochloric acid. The earlier stages in the breaking up of proteins are rapidly passed over and peptones quickly converted to amino-acids and related bodies. These end-products may be briefly classified as follows: (1) Ammonia; (2) cystin; (3) derivatives of the aliphatic series—glycocoll, alanin, serin, leucin; (4) dibasic acids—aspartic and glutaminic acids; (5) carboxylic derivatives—tyrosin and phenylalanin; (6) pyrrolidin derivatives—prolin, tryptophan; (7) hexone bases—lysin, histidin, arginin. The splitting up of proteins under trypsin is more complete after the normal preliminary peptic digestion, but not so complete as the breaking up which occurs on boiling with hydrochloric acid. In each case the change is one of hydrolysis. There is no reason for believing that the intermediary, primary, and secondary proteoses, peptones, etc., are not alike in gastric and pancreatic hydrolysis.

The *amylopsin* of the pancreatic juice is identical in its action to the ptyalin of the saliva—it changes starch to maltose and dextrins but with greater energy.

Lipase splits neutral fats into glycerin and corresponding fatty acids. The latter combine with alkalies of the pancreatic juice to form soaps. In this process the bile is intimately associated; the bile acids and lecithin acting as coferments. It was formerly thought that only a portion of the fat was thus changed, and that the fatty acid was united to some of the bases present in the pancreatic juice, forming a soap and emulsifying the remainder of the fat, which was then absorbed as fine globules. Recently another view has become prominent, which supposes all the fat to be converted into soluble glycerin and fatty acids, which are absorbed as such and later recombined as neutral fats in a fine state of emulsion called *molecular fat*.

Bile.—The bile is partly an excretion and partly a secretion. The quantity formed a day in man is from 500 to 800 c.c. It consists of water, salts, bile pigments, bile acids,

cholesterin, lecithin, neutral fats, soaps, traces of urea, and a mucilaginous nucleo-albumin wrongly called mucin. The color of bile in carnivora is a bright golden red, due to the pigment bilirubin, while in herbivora it is green as the result of the pigment biliverdin. The color of the human bile varies from a yellow to a dark olive. It is feebly alkaline, and has a specific gravity of 1010 to 1050. *Biliverdin* $(C_{16}H_{18}N_2O_4)$ is an oxidation product of *bilirubin* $(C_{16}H_{18}N_2O_3)$. They are detected by *Gmelin's reaction*, which consists in bringing the solution to be tested in contact with fuming nitric acid, when a series of color changes result. The bile pigments originate in the liver from hemoglobin. They are mixed with the food in its passage along the intestine, and are partly reabsorbed and carried back to the liver in the portal blood. The bile acids are found as the sodium salts of *glycocholic* and *taurocholic acid*. Both are present in human bile, and may be detected by *Pettenkofer's reaction*, which consists in adding to the liquid to be tested a few drops of a 10 per cent. solution of cane sugar, and then, carefully, strong sulphuric acid. The temperature must be kept below 70° F. If bile salts are present a violet ring is formed at the junction of the liquids, which is due to the formation of a substance known as *furfurol*. The latter reacting with the bile salts gives the color. The bile salts are reabsorbed, partially at least, and again given off by the liver. The value of this process is not known unless it is to economize material, since the bile salts serve to hold the excretion cholesterin in solution, which is constantly present in the bile, and serve also to assist in the absorption of fats from the intestine. *Cholesterin* $(C_{27}H_{46}O)$ is eliminated by the liver cells and remains unchanged in the feces. It is a crystallizable, insoluble substance, found particularly in the medullary substance of nerve fibers. The nucleo-albumin of the bile is formed by the cells of the ducts and gall-bladder, and gives to bile its mucilaginous character. Bile has indirectly feeble antiseptic powers, and to some extent retards putrefactive changes in the intestine, and it also neutralizes the acid chyme from the stomach. The role played by bile in digestion is the preparation of fats for absorption. This it does in conjunction with the pancreatic juice. Neutral fats, after being melted by the heat of the body, are converted partially to

glycerin and fatty acids by the action of lipase. The fatty acids combining with sodium form soaps. There now simultaneously results a splitting up of the neutral fat, which remains into minute globules which have no tendency to run together. This process, known as the emulsification of the fat, is an obscure, physical process. Although pancreatic juice is in itself sufficient to emulsify fats, the process is greatly accelerated by the presence of bile or bile salts. Possibly this is due to a well-known characteristic of bile, that of diminishing surface tension when added to aqueous solutions. Bile salts, furthermore, have the capacity of dissolving soaps, and a solution of soaps in bile salts, in turn, dissolve free fatty acids. Through this interaction the amount of fat split is increased twofold or threefold.

In some diseases of the pancreas, fat and fatty acids appear in the stools. The same may be true when bile is prevented from entering the intestine through obstruction or in case of biliary fistula, but in the latter case, at least, the patient's health is not affected. The offensive odor of the feces in the latter cases is very likely due to a coating of the food with fat, preventing the action of digestive enzymes and so giving free reign to the activity of bacteria.

When bile comes in contact with chyme a precipitate is formed which is a salt-like compound of protein and taurocholic acid. Bile acids and mucin are also thrown down. These are redissolved by further additions of bile.

Succus Entericus.—The intestinal juice is supposed to be the product mainly of Lieberkühn's crypts. It is a thin, yellowish liquid of alkaline reaction and generally turbid in appearance. It contains the proteins, serum albumin and serum globulin. The inorganic salts are chiefly sodium chloride and sodium carbonate. The quantity formed per day has been estimated to be two or three liters. It has little digestive action except on starch.

Extracts of the walls of the small intestine, however, contain four or five different enzymes which have a profound influence upon intestinal digestion:

1. Enterokinase, which activates trypsinogen.

2. Erepsin, an enzyme which acts especially upon deutero-proteoses and peptones, converting them to amino-acids.

3. Inverting enzymes, which convert disaccharides into mono-saccharides. They are three in number—maltase, invertase, and lactase.

4. Nuclease, an enzyme which acts upon nucleic acids.

5. Secretin, formed in the intestinal mucosa as prosecretin and changed to secretin by hydrochloric acid. It is not an enzyme but comes under the class of bodies known as hormones.

Digestion in the Large Intestine.—Here the secretion is composed mainly of mucus, is scanty, alkaline in reaction, and has no enzymes of its own. Digestive changes occur, however, for some time, and are due to enzymes brought down from above. Extensive bacterial decomposition takes place.

Bacteria may be found in any portion of the intestinal tract, and their activity is always involved in ordinary digestion. But it is not essential to health in mammals. Guinea-pigs removed from the mother by Cesarean section, reared aseptic-ally, and fed on sterile milk grew as fast as those reared in the ordinary way. The alimentary canal remained free from bacteria. Chickens, on the other hand, reared under similar conditions lived only eighteen days. It is possible that the vegetable food requires the aid of bacteria to insure its proper digestion.

As the result of the action of bacteria on proteins there are formed indol, phenol, and skatol. These are excreted in the feces and partly reabsorbed, conjugated with sulphuric acid, and excreted in the urine. Indol, in this way, appears in the urine as indican. In some animals a cellulose-destroying enzyme leads to the formation of sugar, but in man, although cellulose is to some extent destroyed, no sugar is formed. The contents of the large intestine are usually acid, but the wall itself is alkaline in reaction.

Feces.—The feces vary in composition and amount with the nature and the quantity of the food. On a mixed diet the amount in twenty-four hours varies from 100 to 500 grams in weight. Its constituents are indigestible materials, un-digested foodstuffs, intestinal secretions, products of bacterial action, cholesterin, excretin, mucus, pigment, salts, gases, and microörganisms. Among the products of bacterial action are *indol* (C_8H_7N) and *skatol* (C_9H_9N), which are crystallizable

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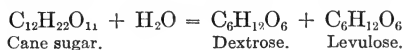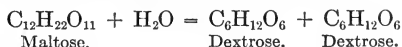bodies giving odor to the feces. The color is due to *hydrobilirubin*.

Summary of Digestion.—**Protein food** is but slightly altered in the mouth, and only in a mechanical way. The muscle fibers of meat, for instance, are crushed, and their connective-tissue sheaths broken by the action of the teeth, thus becoming somewhat lighter in appearance. Mixed with saliva, which has no digestive action on these foodstuffs, they are passed into the stomach and brought under the influence of the gastric juice. By the combined action of the hydrochloric acid and the ferment pepsin proteins pass through a series of steps which consist essentially of a taking up of water and a breaking into simpler bodies. *Syntonin*, the first product formed, becomes converted into *proto-* and *deuteroproteoses*, and *peptones*. But the food does not remain in the stomach long enough for all the proteins to be changed to peptones. Some pass through entirely unchanged, while others have reached various stages of digestion.

In the intestine the energetic action of the trypsin changes those proteins that reach it to peptones more quickly than does the gastric juice, the intermediate stage of the primary proteoses being omitted. The peptones are still further changed to comparatively simple *amino bodies* and *nitrogenous bases*. The most important of these are leucin and tyrosin. Finally, in the large intestine proteins that still remain are attacked and decomposed by bacteria, but some escape and are ejected in the feces.

Albuminoids.—These bodies undergo changes analogous to those of proteins; the conversion in the stomach reaches chiefly only the gelatose stage, but the pancreatic juice produces gelatin peptones.

Carbohydrates.—The time that starches remain in the mouth is too short for the ptyalin of the saliva to produce any very great changes, but the digestion may continue for some time within the stomach. The acidity of the gastric juice later stops all carbohydrate digestion, and it is not until the food reaches the intestine that the amylopsin of the pancreatic juice actively begins the conversion of starches. The action of ptyalin and amylopsin is identical. Starch is modified into *soluble starch*, and then begin a series of hydration changes

during which the starch molecule is split into *maltose* and *erythrodextrin*. The latter again into *maltose* and *achroödextrin;* achroödextrin again into *maltose* and a still *simpler dextrin*, and so on until only *maltose* results. In the intestinal secretion there is an enzyme which aids amylopsin in the conversion of starch to maltose. The sugars thus formed and others, eaten as such, are by means of inverting enzymes (*invertase* and *maltase*) of the intestine changed to monosaccharides. This is illustrated by the following equations:

$$C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6$$

Maltose.   Dextrose.   Dextrose.

$$C_{12}H_{22}O_{11} + H_2O = C_6H_{12}O_6 + C_6H_{12}O_6$$

Cane sugar.   Dextrose.   Levulose.

It has been found that cane sugar may also be converted to dextrose and levulose in the stomach. Carbohydrates that escape digestion and absorption and reach the large intestine are largely destroyed by bacteria.

Fats.—These are but slightly changed before they reach the fat-splitting ferment, steapsin, of the pancreatic juice, except that they are separated from the connective tissue by the action of the teeth and proteolytic enzymes, and are partially melted by the heat of the body in the stomach. In the intestine fats are changed to *glycerin* and a corresponding *fatty acid*. The latter may unite with bases present to form soaps, which emulsify the remaining unaltered fat. According to one view, fat is mainly absorbed in the form of an emulsion. According to another and later view, all of it is converted to fatty acid and glycerin, absorbed as such, and then recombined to form neutral fat. While considering the action of digestive juices, it is interesting and important to remember that the ferment rennin of the gastric juice *coagulates milk*. The casein of the milk under the influence of the enzyme undergoes a hydrolytic cleavage, with the formation of paracasein and whey protein. Paracasein unites with calcium to form the insoluble curd. The action of rennin is confined to milk, and the value of the curdling action lies probably in an easier conversion of the milk proteins in the coagulated form. The digestion of milk after coagulation is carried on by the enzymes of the gastric and pancreatic juices.

Self-digestion of the Alimentary Tract.—Why the stomach or any other portion of the intestinal tract brought into contact with digestive juices is not destroyed has given rise to much discussion. Normally, self-digestion does not occur, but if an animal is killed while in full digestion and the body is kept warm, the stomach will be destroyed. This has been found to take place in human bodies. If a portion of the stomach is deprived of its blood supply, that portion will be attacked and a perforation of the stomach may result. The immunity of the stomach to the gastric juice has been explained in a number of ways, but not satisfactorily. It has been said that the epithelial lining of the stomach prevents the absorption of the gastric juice, but this explanation raises the question why the living epithelial cells are immune.

The secretion of mucus forming a protective coating for the stomach is an inadequate explanation, owing to the difficulty of conceiving such a means of protection to be as perfect as it is. Another theory which holds the alkaline blood to neutralize the acid of the stomach as it is formed cannot be applied in the case of the intestine, where the digestive juice is alkaline. An explanation is at present impossible. All that can be said is that the immunity of the intestinal tract is due to the fact that it is alive. It has been shown by Neumeister that a living frog's leg is not digested by a strong pancreatic digestive mixture of weak alkaline reaction, because in this case the cells are not killed. Bernard introduced the hind leg of a living frog into a dog's stomach through a fistula. It was digested. But in this case the cells of the frog's limb were first destroyed by the acid.

There is some reason for believing that free hydrochloric acid cannot penetrate living cells and free hydrochloric acid must be present before peptic digestion can begin. In some gland cells the enzyme is present within the protoplasm in an inert zymogen form, as in the case of the pancreas. When trypsin is injected under the skin it causes the tissues to break down and ulcerate. Active trypsin may remain for a long time in an isolated loop of small intestine without producing any serious consequences; but if the intestinal wall is previously damaged, not only is the tract itself affected, but soon the liver as well. Few tissues can bear the constant contact of urine

and feces as do the lining of the urinary tract and large intestine. When urine is injected under the skin, or, through rupture of the intestine, fecal matter makes its way into the abdominal cavity, they come into contact with tissues which, though alive, are not adapted to resist them, and so lead to serious consequences. Very suggestive results have been obtained with *extracts from intestinal worms* which spend their entire lives in the digestive secretions. Such extracts contain substances, precipitable by alcohol, which inhibit the action of either pepsin or trypsin as the case may be. Fibrin may be impregnated with the precipitated "antienzyme," which then becomes resistant to the digestive action of the alimentary secretions. These experiments are very suggestive, even though it has not been possible to obtain similar bodies from the intestinal mucous membrane. The antitrypsin which is present in the blood has the same properties as the antitrypsin of intestinal worms. Finally, there has been found in the blood of some animals an antikinase, which inhibits not the action of trypsin but of enterokinase.

Reaction of Intestinal Contents.—The many confusing results obtained by different observers in testing the reactions of intestinal contents are due partly to the indicators used. Methyl orange, which is the most stable of the indicators usually employed, is not affected by weak organic acids, but reacts acid to inorganic and the stronger organic acids, like lactic, acetic, and butyric acid, and alkaline to the salts of the weaker acids, such as sodium carbonate and bicarbonate. Phenolphthalein is very sensitive to acids, even to weak organic acids like fatty acids and to carbonic acid. Litmus lies intermediate in sensitiveness as an indicator.

The chyme which comes through the pylorus is acid and mingles in the duodenum with the alkaline bile and pancreatic secretion. In time, therefore, the acid reaction in the duodenum, as tested with litmus, becomes less or even weakly alkaline. But it soon becomes acid again, and the acidity increases again for a while as the food passes along the intestine. In the region of the ileocecal valve the contents may be neutral or actually alkaline. To phenolphthalein the reaction is acid throughout the small intestine, while methyl orange shows an alkaline reaction except at times in the duodenum. When

active digestion has ceased the reaction becomes acid to all three indicators. The differences in reaction are always slight, and there is never a great preponderance of either hydroxyl or hydrogen ions.

There is no doubt that the acidity of the gastric juice forms an important check on bacterial activity in the alimentary tract, separating the bacteria-infested regions of the mouth and pharynx from the small intestine. But even under normal conditions some active microörganisms of various kinds can be obtained from the stomach. Bacteria which form acid products are less affected by the acid gastric juice than the putrefactive bacteria which are accustomed to an alkaline medium. Normal guinea-pigs fed with cholera bacilli were unaffected. But if the gastric juice was neutralized before administration of the bacilli the guinea-pigs died. By some the bactericidal action of the stomach is considered its chief function, and stress has been laid upon the fact that the stomach in both dogs and man has been removed, leaving, after years, every other organ in perfect health. But it has also been shown that dogs without stomachs might be fed on putrid meat with no harmful effects greater than in a normal dog. So that if an animal can get along without the digestive functions of the stomach, it can, likewise, get along without the bactericidal action of the stomach contents.

QUESTIONS ON CHAPTER III

Define a foodstuff.
Give classification of foodstuffs and describe each group.
Discuss enzymes; define and give general properties.
Discuss manner of action of enzymes.
What reason is there for the belief that enzymes act by hydrolysis?
In what sense may oxygen be called a food?
Describe the saliva. What is its composition?
What is the function of saliva?
Give detailed steps of the action of ptyalin on starch.
What is the action of acid on the activity of ptyalin?
Why is starch more easily digested when cooked than when raw?
Describe the gastric juice.
What are the proofs that the acid of the gastric juice is free hydrochloric acid?
How is the reaction of the blood and the urine affected during active secretion of gastric juice?
What is pepsin?
Give detailed steps of the action of hydrochloric acid and pepsin on proteins.

Explain the action of the ferment rennin in detail.

Describe the curd of human milk.

In what ways are fats and albuminoids changed in the stomach?

Where does the food undergo its greatest digestive changes?

Describe the pancreatic juice. Its composition.

How does the action of trypsin differ from that of pepsin?

What is the source of leucin and tyrosin?

Compare the action of amylopsin and ptyalin.

What is lipase?

What is the action of steapsin on fat?

Describe the bile.

What causes the difference of the color in the bile of herbivora and carnivora?

How are the bile pigments detected?

What is the source of the bile pigments?

What is their fate?

What are bile acids? How detected?

Give fate of bile acids. What is their function?

Describe cholesterin.

What makes the bile viscid?

How is the intestinal secretion obtained?

Describe the succus entericus.

Describe the secretion of the large intestine.

What is the reaction of the large intestine?

What is the reaction due to?

What changes do bacteria produce in the intestine?

Describe the feces.

What substances give odor and color to the feces?

Summarize briefly the entire process of digestion.

Discuss fully the absence of self-digestion of the alimentary tract.

Discuss the reaction of the intestinal contents.

Discuss the bactericidal value of the gastric juice.

CHAPTER IV

ABSORPTION

General Principles.—When food in the intestinal canal has undergone its digestive changes it is absorbed. The alimentary canal from esophagus to rectum consists of a single layer of columnar epithelial cells placed on a basement membrane. The soluble diffusible constituents of the food on one side and the blood on the other side seem to offer favorable conditions for filtration and osmosis. But it has been proved that the *activity* of the *epithelial cells* is an important factor in absorption.

1. Substances are absorbed from the intestine having the same, less, or greater osmotic tension.

2. Sugar and peptones, which are less diffusible than sodium sulphate, are absorbed more rapidly.

3. Non-dializable substances like egg albumin may be absorbed.

4. Some substances like peptone are changed in their passage through the intestinal wall.

There are *two paths* which absorbed products may take. They may pass directly into the blood of the capillaries and so into the portal system, in which case they are taken to the liver, or they may pass into the lacteals of the lymphatic system, forming chyle. In this case they pass through the thoracic duct to enter the general circulation at the junction of the left internal jugular and subclavian veins. *It will, therefore, be noted that the blood is the final objective point by each path.*

Absorption from the Stomach.—The amount of absorption in the mouth is quite insignificant and that from the stomach is not very marked. Sugars, peptones, and proteoses may be absorbed with difficulty. The same is true of water, which is usually rapidly passed into the duodenum. Alcohol is absorbed more rapidly and so are extractives of meat, which form an important part of most thin soups and of beef tea.

Salts, like sodium iodide, are not at all absorbed in dilute solutions, but when the concentration reaches 3 per cent., absorption becomes pronounced. Normally salts never reach this degree of concentration. It has been found that the absorption of sodium iodide is greatly increased by mustard, pepper, and alcohol, which act either by congesting the mucous membrane or perhaps by stimulating the epithelial cells to greater activity.

Absorption from the Small Intestine.—The food in its passage along the intestine moves slowly, requiring from nine to twenty-three hours after ingestion to appear at the end of the small intestine. The latter, moreover, presents a vast surface for absorption by reason of the villi and the valvulæ conniventes. Both of these structures favor absorption. As a matter of fact, 85 per cent. of the protein has been found to disappear. That proteoses and peptones are absorbed directly by the blood is shown in ligating the thoracic duct, which does not interfere with their disappearance. Nevertheless, they do not appear in the blood as such, and if present, act as poisonous bodies which cannot be used by the tissues and are immediately excreted by the kidneys. It is probable that they are changed in their passage through the epithelial walls under the influence of erepsin. The direct way of determining the facts would be to examine the blood during the absorption of proteins; but the flow of blood is so great, the quantity of absorbed products so small, and their removal by the tissues probably so rapid, that certain results have not been ascertained. It may be accepted, however, that during absorption there is an increase in the nitrogenous substances of the blood which are not precipitated by tannic acid, and are, therefore, neither native proteins nor proteoses. Urea accounts for one-half of the increase, so that the rest is probably in the form of amino acids.

Carbohydrates, which are changed to diffusible sugars, dextrose and levulose, are also absorbed directly into the blood, and as a consequence the portal vein has been found to show an increased percentage of sugar after meals. The lymph of the thoracic duct shows no such increase unless excessive quantities have been taken.

Fats, it is conceivable, may be absorbed in an emulsified condition, or, as glycerin, fatty acids, and soaps. Experi-

mentally, in some animals at least, it has been found that the greater part of the fat (60 per cent.) is passed through the epithelial cells and through the stroma of the villi to the central lacteal, which is the beginning of the thoracic duct. The remainder is absorbed by the blood as fatty acid and glycerin. There is, very likely, a synthesis of some of the latter substances in the body of the epithelial cells into neutral fat. The absorption of water and salts by the small intestine is very active, but there is also a secretion of water back into the intestinal lumen, so that the contents remain of the same fluid consistency. Water and salts are absorbed directly by the blood unless excessive quantities are taken, when a portion passes through the lymphatic system, accelerating the flow of the chyle. Seventy to 83 per cent. of the combined jejunum and ileum in dogs have been removed without effecting metabolism, showing a wonderful efficiency as a digesting and absorbing organ. In man fully one-half of the small intestine has been removed with ultimate recovery.

Absorption from the Large Intestine.—The absorption from this part of the alimentary tract is considerable, as is shown by changes in its contents, which, entering at the ileocecal valve in a fluid state, are converted into solid feces. Of the 15 per cent. protein present some is absorbed and some is destroyed by bacterial action. The absorptive powers of the large intestine have been illustrated by the injection of nutrient enemata consisting of egg albumin, salt, and milk fat. In this case, however, the antiperistaltic movements of the large intestine may pass the food back through the ileocecal sphincter into the small intestine, where an important part of the preliminary digestion and absorption may occur. Furthermore, remnants of proteolytic, amylolytic, lipolytic, and inverting enzymes may have been passed into the large intestine, where they continue their work.

QUESTIONS ON CHAPTER IV

What conditions are present in the alimentary canal that favor filtration and osmosis?

Give proofs that epithelial cells are active during absorption.

What paths may absorbed products take in their passage into the blood?

Discuss the absorption that takes place in the stomach.

What conditions in the small intestine favor absorption?

What is the path taken by absorbed protein?

In what form do proteins appear in the blood?

Where are they changed?

What is the fate of peptones and proteoses injected into the blood?

Give the path taken by absorbed carbohydrates.

How are fats absorbed?

Trace the path of fats from the intestinal lumen into the blood.

Discuss the absorption of water in the small intestine.

What paths do water and salts take in absorption?

Discuss the absorption that takes place from the large intestine.

What change in the consistency of the contents of large and small intestine is brought about by absorption?

CHAPTER V

THE BLOOD

THE blood, a chemically complex fluid contained within the vessels of the body, has been recognized from the earliest times as indispensable to the life of man. An excessive hemorrhage prostrates, enfeebles, and may cause death. This becomes evident when it is known that the blood carries to the tissues material for their growth and repair, and removes from them matters that have become effete. It equalizes the temperature of the body, and maintains uniform imbibition relations between the cells. It is an internal medium that bears the same relations to the tissues that the outer world does to the entire body. It forms in total from 5 to 7.7 per cent. of the body weight, so that a man of 170 pounds will possess over 13 pounds of blood, or nearly 6 quarts. In given individuals it does not vary through any wide limits. Variations that are brought about by loss of water as by perspiration or by a gain of water, as through the ingestion of excessive quantities of water, are compensated for by a passage of fluid from or to the tissues. In starvation the quantity and the quality of the blood are maintained at the expense of the other tissues.

An *estimation* of the *amount* of blood of an animal is made by measuring directly as much as will escape from the vessels. The latter are then washed out with normal saline solution, and the tint of the washing is matched by diluting a given quantity of normal blood. This process is repeated after carefully mincing the entire body. The blood in the washings may be calculated by knowing the dilution of normal blood required to match it. This, added to the amount measured directly, gives the total quantity. It is distributed in the body as follows:

One-fourth in the heart, lungs, large arteries, and veins.
One-fourth in the liver.
One-fourth in the skeletal muscles.
One-fourth in the remainder of the body.

Composition of Blood.—The blood consists of a fluid *plasma* (*liquor sanguinis*), in which are suspended cells called *blood corpuscles. It may be regarded as a tissue of which the intercellular matrix is a fluid.* Freshly drawn, it is of a bright scarlet color when taken from the arteries or pulmonary veins, but crimson when taken from the systemic veins. This is the result of different oxidation stages of the pigment hemoglobin, which is contained in the red corpuscles. The blood is opaque, caused by the fact that its solid elements oppose the transmission of light by reflecting it back from their surfaces. In various ways, as by the addition of ether, bile, excess of water, by freezing and thawing, etc., the coloring matter may be driven from the corpuscles into solution in the plasma, leaving a delicate, colorless cell body, through which the light passes readily. The blood is then transparent, and is known as laky blood. The specific gravity varies from 1041 to 1067, according to age, sex, state of health, meals, exercise, and sleep. Its slightly alkaline reaction to litmus is due to the phosphates and carbonates of the alkaline metals. Estimated as sodium carbonate, it is equal to 0.35 per cent. Ordinary litmus paper cannot be used in testing the reaction of the blood, owing to the fact that it stains red with hemoglobin. Soaking in saturated salt solution covers the paper with a layer of salt that holds the corpuscles, which may then readily be washed off.

Reaction of Blood.—The question of the reaction of the blood has, with the development of physical chemistry, received far greater definiteness. It, as well as most of the normal body fluids, is, so far as the relative content in H and OH ions is concerned, neutral. Ordinary indicators are affected differently by the same solutions. Thus phenolphthalein reacts neutral with blood instead of alkaline, as does litmus. In determining the alkalinity of the blood by titrating with weak tartaric acid, this acid is sufficiently strong to drive the sodium out of its weak combination with carbonic or phosphoric acid. This method indicates, therefore, the dissociable

sodium of the blood rather than the relative number of H and OH ions. These are present in blood to about the same extent as in water. The blood as it exists in the body always contains a certain amount of CO_2, $NaHCO_3$, Na_2HPO_4, and also sodium in combination with protein, which from this point of view is a weak acid. These constituents are in an unstable equilibrium, so that a considerable amount of acid or alkali may be added without approximately altering its neutral reaction. An important distinction is, therefore, to be borne in mind, that is, the *potential* or *titration reaction* as contrasted with the *physicochemical* or *true reaction*.

Blood has a salty taste, and a peculiar, characteristic odor. The temperature is about 98.9° F., but probably is higher in the internal parts of the body.

Corpuscles.—The corpuscles of the blood are of at least three kinds—*red corpuscles (erythrocytes)*, *white corpuscles (leukocytes)*, and *blood plates (microcytes)*. The **red cells** may be put at 5,000,000 per c.mm. for males, and at 4,500,000 for females, as an average number. Their number varies with the constitution, nutrition, manner of living, and age of the individual. They are most numerous in the embryo and young. In the adult their number is at a minimum after meals; it is increased during menstruation, and decreased during pregnancy. *Change of altitude* has been found to exert a most remarkable influence. A mountain life has been found to raise the average number to 8,000,000, and to increase the contained hemoglobin as well. A return to a lower level brings back the blood to its normal state. A diminished pressure of oxygen in the blood, whether produced by high altitudes or by the actual loss of blood, stimulates to greater activity the tissues that form new corpuscles. When viewed under the microscope individually, each corpuscle is of a faint yellowish color. Each consists of an extensible, protoplasmic material known as *stroma*, which gives shape to the corpuscle and holds the hemoglobin. The latter, forming 90 per cent. of the solid matter of the corpuscle, is held in some weak chemical combination with the stroma, since its behavior within the corpuscle differs from that when separate.

Hemoglobin is a member of the group of combined proteins. It may be separated in various ways into a protein body,

globin (96 per cent.), and a simpler pigment, *hematin* (4 per cent.), together with other bodies whose nature is unknown. If the decomposition takes place in the absence of oxygen, *hemochromogen* is formed instead of hematin. It is the hemochromogen that gives to hemoglobin its peculiar power of taking up oxygen into loose chemical combination. *There are* 14 *grams of hemoglobin to every* 100 *grams of blood, so that a man weighing* 68 *kilos has* 750 *grams of hemoglobin distributed among* 25,000,000,000,000 *corpuscles, giving a superficial area of about* 3200 *square meters.* This is important from a *respiratory* point of view, as the entire surface is practically exposed to the *absorption* of oxygen. Hemoglobin will take 1.59 c.c. of oxygen to each gram weight, and form in so doing a compound known as *oxyhemoglobin*. The latter, if placed in an atmosphere which is deficient in oxygen, will be converted by the loss of oxygen to hemoglobin. Hemoglobin has the power of combining with a number of other gases. With *carbon monoxide* it unites in the proportions of one volume to one of hemoglobin, forming *carbomonoxide hemoglobin*, which is more stable than oxyhemoglobin, so that it is not easily converted into ordinary hemoglobin. *This explains the fatal effects produced by breathing illuminating gas, which contains carbon monoxide as a constituent.* The oxygen of the air is prevented from uniting with hemoglobin, and thus produces asphyxia. *Nitric oxide* (NO) produces a still more stable combination. Carbon dioxide (CO_2), however, which in its reaction with hemoglobin produces *carbohemoglobin*, unites with a different part of the hemoglobin molecule, since it does not interfere with the absorption of oxygen. *Thus is explained the action of this gas as an anesthetic.* It has been suggested that the carbon dioxide unites with the protein portion, and it makes possible the transportation of carbon dioxide by hemoglobin from the tissues, where it is given off as a waste product, to the lungs, where it is removed from the body. The most characteristic feature of hemoglobin is the presence of *iron*, which amounts to about 0.47 per cent., so that an estimation of the iron of the blood would be a method of determining the amount of hemoglobin. This element remains a part of hematin when hemoglobin is decomposed, and upon it depends the affinity of hemoglobin for oxygen. One atom of iron will take

up one molecule of oxygen. Both oxy- and ordinary hemo-globin are crystallizable. A good method is to shake the blood in a test-tube until it becomes laky, and then place it on ice until the crystals form. They have different forms in different animals—for example, those of man and most mammalia are rhombic prisms; of the squirrel, rhombic plates; and those of the guinea-pig, tetrahedra. These crystals are soluble in water, but do not dialyze.

Identification of Blood Stains.—Hematin unites with hydro-chloric acid (HCl) to form *hemin*, the crystals of which are of the greatest importance in the *identification of blood stains.* Scrapings from the stain are placed on a glass slide, and a drop of a 1 per cent. solution of sodium chloride (NaCl) is added. Heat over a gentle flame, avoiding ebullition until the water has nearly evaporated. Then quickly add one or two drops of glacial acetic acid, cover with a cover-glass, and again warm until the acid has nearly disappeared. When cool, micro-scopic, characteristic, brown crystals are deposited. Together with the *spectroscopic test* they indicate positively the presence of blood. The presence of cells of certain size and non-nucleated ones will exclude the blood of certain animals, but it is not sufficient evidence of human blood. *Mammals have non-nucleated cells.*

A method of considerable medicolegal value in the detection of human blood rests upon the formation of specific precipitins. The technique of this method is as follows: The blood stain is macerated in isotonic saline and filtered. The clear filtrate is divided into two parts, each of which is placed in a test-tube. To one of these is added rabbit's serum immunized to human serum; the other is left as a control. Into a third test-tube is placed some of the precipitating serum alone, and into a fourth tube a mixture of precipitating serum and some indifferent serum of an ox in physiological saline. These four tubes are placed in an incubator at body temperature for an hour. If the stain be due to human blood a cloudiness will develop in the first tube, while the others remain clear. This method fails to differentiate human blood from ape's blood, and must be used with great caution, owing, in some cases, to the apparent formation of antiprecipitins.

Solutions of hemoglobin and compounds derived from it

give characteristic absorption bands. The spectrum of a dilute solution of oxyhemoglobin shows two dark bands, both between the lines D and E. That nearer the red end of the spectrum, or *alpha band,* as it is called, is darker, narrower, and more distinct than the other, or *beta band.* The distinctness and width of the bands vary with the density of the solution. With very dilute solutions only a faint alpha band is present; with stronger solutions the bands grow wider, fuse, and finally shut off all light. The orange is the last to disappear. If a solution of oxyhemoglobin is converted to reduced hemoglobin by the addition of *Stokes' reagent* (an ammoniacal solution of a ferrous salt), only one absorption band is seen, called the *gamma band,* which lies between the lines D and E.

The length of life of a red blood corpuscle is not known. Since hemoglobin forms the mother substance of the bile pigments which are continually being passed from the body, and also since the corpuscles are non-nucleated, it is believed that they are continually undergoing disintegration in the bloodvessels. They are replenished by special corpuscle-forming or hematopoietic tissues, the process of production being known as *hematopoiesis.* The red marrow of the bones is the most marked example of such tissue. Here groups of nucleated colorless cells known as *erythroblasts* undergo karyokinesis, and the daughter cells, after forming hemoglobin in their cytoplasm, are nucleated corpuscles which in time extrude their nuclei and are forced by the growing tissue into the blood stream. In the embryo the liver and the spleen also produce new red corpuscles.

White Blood Cells.—These are variously classified. Ehrlich makes three divisions—*oxyphiles* or *eosinophiles,* whose granules are stained with acid stains; *basophiles,* which stain only with basic stains; and *neutrophiles,* which stain only with neutral dyes.

A simpler classification may be made:

1. *Lymphocytes,* small, having a round vesicular nucleus and scanty cytoplasm.

2. *Mononuclear leukocytes,* large, having a vesicular nucleus and abundant cytoplasm.

3. *Polynuclear leukocytes,* large, with nucleus divided into lobes or into distinct parts.

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4. *Eosinophile cells*, like the last, but with cytoplasm filled with coarse granules.

It is possible that the members of the last classification may be progressive stages in the growth of a single kind of cell, the lymphocyte forming the youngest, while the polynuclear cell forms the oldest stage. Leukocytes show ameboid movements which enable them to move from place to place (therefore called *wandering cells*), and even to pierce the walls of the bloodvessels and get into the lymph spaces. This process is known as *diapedesis*. Their number is put at about 7500 per c.mm. A marked increase in number (*leukocytosis*) is seen in leukemia.

Function of Leukocytes.—A number of suggestions have been made as to this:

1. They protect the body from disease by ingesting pathogenic bacteria (phagocytosis). Such cells are known as *phagocytes;* or they may guard the body by the formation of *protective proteins* which destroy disease germs and their toxins.

2. They aid in the absorption of fats and peptones.

3. They take part in the coagulation of the blood.

4. They help to maintain the normal composition of the blood in regard to its proteins, since the latter are not all formed directly from absorbed food. They do this by undergoing disintegration in the blood and by active metabolic changes which are indicated by their cytoplasm in the formation of zymogen granules. Leukocytes multiply by karyokinetic division, and are also newly formed in the lymph glands and lymphoid tissue.

The **blood plates** are small circular or oval bodies of homogeneous structure and of variable size. Their number is about 250,000 per c.mm. They are not independent cells, and therefore soon disintegrate. Composed of the same substance as the nuclei of leukocytes, they are often regarded as nothing more. They take part in the coagulation of the blood.

Plasma.—The plasma, which is a viscid, straw-colored fluid of a specific gravity of 1030, may be obtained in a number of ways: The blood may be cooled, in which case coagulation takes place slowly and the corpuscles have time gradually to sink to the bottom of the vessel. The corpuscles having a specific gravity of 1088 are the heaviest components of the blood. When blood is received directly into neutral salt solu-

tions, as sodium or magnesium sulphate, it will not clot. The corpuscles may then be allowed to sink, or they may be centrifugalized off. The method of action of the salt is not known.

Peptones and albumoses, when injected into an animal, will prevent the clotting of its blood for a long time. But peptone added to blood already shed has no such effect. The action of the peptone in the body is explained in that it causes a rapid destruction of leukocytes. This sets free two substances—a *nucleoprotein* and *histon*. The first takes part in the formation of *fibrin ferment*, which is destroyed by the liver, while the second, which is known to be antagonistic to the coagulation of the blood, is left in the bloodvessels. The addition of *oxalate solutions* by precipitating the soluble calcium salts will prevent coagulation.

Plasma consists of water, at least three kinds of simple proteins, combined proteins, extractives, and salts. The simple proteins are *serum albumin, serum globulin,* and *fibrinogen.* The *serum albumin* is separated from the other two by saturation with magnesium sulphate, which leaves it in solution, while it precipitates the globulins. It may be brought down in a neutral or acid medium by heat, which gives three different coagulations—at 73°, 77°, and 84° C. respectively, indicating three kinds of serum albumin. In man it forms about 4.52 per cent. of the solids. Its source is the absorbed foodstuffs. *Serum globulin (paraglobulin)* is coagulated at 75° C. In man it forms about 3.1 per cent. of the solids present, and is more abundant in serum than in plasma, on account of the disintegration of the white blood corpuscles, which takes place during coagulation. Whether this is its sole source is not known. Paraglobulin does not behave like a chemical individual. Portions of it are precipitable by carbon dioxide, and other portions not. Furthermore, a one-third saturation with ammonium sulphate will bring down a fraction of the total protein only. This portion is now known as *euglobulin.* A less easily precipitable portion, *pseudoglobulin,* will not come down until one-half saturation with ammonium sulphate has been reached.

Fibrinogen is another globulin coagulating at from 56° to 60° C. It is present in human blood to the extent of 0.22 to 0.4 per cent. Its nutritive value to the body and its source

are unknown. It is indispensable to the coagulation of the blood.

The extractives of the plasma include fats, sugar, urea, lecithin, cholesterin, and gases. The inorganic salts are peculiar in their distribution, inasmuch as the plasma contains an excess of sodium salts, while the corpuscles contain an excess of potassium salts.

Coagulation or Clotting.—After the blood has escaped from the vessels of the body it exhibits its most peculiar property —that of *clotting*. If the blood is caught in a beaker, it is at first perfectly fluid, but soon becomes viscous and sets into a jelly. As the clot shrinks in size it presses out a clear, faint yellow liquid called *blood serum*, which increases in quantity until at the end of about an hour it is sufficient in amount to float the clot. The latter becomes separated from the sides of the vessel. The appearance of the clot or *crassamentum* is due to the formation in the plasma of fine fibrils which extend in every direction and which gradually contract and enclose in their meshes the various corpuscles. The process may be indicated by diagram as follows:

```
                          Blood.
                            |
              ┌─────────────┴─────────────┐
          Plasma.                      Corpuscles
             |
       ┌─────┴─────┐
    Serum.       Fibrin.                   |
                    |                       |
                    └──────────┬───────────┘
                            Clot.
                              |
                              |
                       Clotted blood.
```
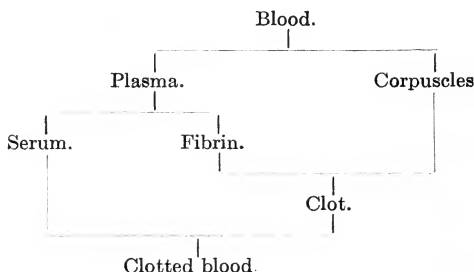
When coagulation has been retarded for some time, the red corpuscles have time to sink from the surface, producing after coagulation a yellow layer which is known as the *buffy coat*. Many leukocytes, owing to their ameboid movements, escape from the meshes of the clot. If the blood, while it is coagulating, is agitated with a bundle of rods, the fibrin is removed as quickly as it is formed, and appears as a stringy white mass on the rods. After this the blood appears normal,

but it has lost its power to coagulate, and is known as *defibrinated blood.*

The **value of clotting** is that it stops hemorrhage. A serious condition is present in some pathological states where the blood will not clot. The *time of clotting* varies in different individuals and at different times. Normally the jelly stage sets in in from three to ten minutes, while the formation of serum requires from ten to forty-eight hours.

Owing to the complexity of the blood, the investigations as to the *cause of clotting* have given rise to many different views. It is universally admitted that the essential part of the clot, the fibrin network, is derived from the fibrinogen which, as the result of the interaction of numerous factors, is thrown out of solution as elongated threads. One of these factors is thrombin or fibrin ferment, which is not present as such in normal blood, but is formed after blood is shed. The addition of the thrombin to a solution of pure fibrinogen gives a clot. In this reaction calcium plays an essential part, for if removed by the addition of sodium oxalate, blood will not coagulate. Its action is intimately related to the formation of thrombin. Thus, if oxalated serum containing ready-formed thrombin be added to an oxalated solution of fibrinogen, clotting takes place. Calcium is regarded as assisting in the formation of thrombin from some antecedent substance which is called prothrombin or thrombogen. Other inorganic or organic substances may also be concerned in the formation of thrombin. Such substances, residing in the various tissues, have been called zymoplastic substances. In pigeons, for instance, shed blood which has not come into contact with the wound clots very slowly, although thrombin, calcium, and fibrinogen are present.

Although spoken of as fibrin ferment, it is doubtful whether thrombin belongs to the group of enzymes. Heating to 65° C. does not destroy thrombin; it merely inactivates it, and its power may be restored by the addition of an alkali. Thrombin does not seem to undergo any essential change in its interaction with fibrinogen, so that it may form a physicochemical rather than a chemical union. The velocity of combination is practically not affected by temperatures between 17° to 38° C., which

would be the case if, in accordance with van't Hoff's law, the reaction were a chemical one.

A conservative statement of the process of coagulation would be as follows: The blood plates and the leukocytes in their disintegration in shed blood yield prothrombin. Prothrombin with calcium salts and possibly zymoplastic substances gives rise to thrombin. Thrombin plus fibrinogen gives fibrin.

That thrombogen has its origin in the leukocytes is shown by the following facts:

1. In microscopic preparations of coagulating blood the fibrin fibrils radiate from broken-down leukocytes and from blood plates.

2. Whatever prevents the disintegration of the white blood cells retards the coagulation of the blood.

Clotting within the bloodvessels may be brought about by the presence of foreign bodies or by injury to the epithelial lining of the vessels. When the clot is confined to the injured area it is called a *thrombus*. General intravascular clotting is brought about by the injection of fibrin ferment, nucleo-albumins, etc.; but this is not accomplished easily, owing to a defensive function for the body exerted by the cells of the liver. Sometimes the blood is rendered less coagulable by the injection of the above substances, constituting the negative phase of the injection. This is explained by the assumption of the predominance of *histon* over *leukonuclein*, both of which are formed by the breaking down of leukocytes. Histon retards the coagulation, while leukonuclein favors it. Normally the blood of the body is prevented from clotting by the integrity of the lining epithelium of the vessels. In the living test-tube experiment, for example, the jugular vein with its contained blood are removed from the neck of the horse, and it is found that the blood under these conditions remains fluid until the epithelial cells of the bloodvessels undergo degenerative changes.

It is not known what percentage of blood may be lost by man through hemorrhage without fatal results, but judging from experiments upon the lower animals, it may be put at about 3 per cent. of the body weight, or one-fourth of the total blood.

Regeneration of the blood takes place rapidly and is completed in from twenty-four to forty-eight hours. After severe hemorrhage recovery is more certain if a solution of sodium

chloride, isotonic with the blood (0.9 per cent.) in man, is injected into the veins. The salt solution increases the blood pressure and makes effective the remaining blood corpuscles, which in normal blood are always in excess of the number absolutely required for respiratory purposes.

The injection of saline solution into the bloodvessels of a normal animal raises the blood pressure, but never above 180 mm. Hg. This limit holds true also when the pressure has previously been lowered by hemorrhage or by section of the cervical cord. The explanation of this fact lies in the manner in which the heart is affected. As soon as the arterial tension reaches its maximal height, the heart beats slower and less vigorously, and the residual blood in the left ventricle increases. This causes a diastolic rise of pressure in the ventricle, which is propagated back through the left auricle, pulmonary circuit, right heart, to the veins. There arises in this way a congestion of the veins and capillaries of the lungs and abdominal organs chiefly. An amount of salt solution equal to four times the normal quantity of blood of the animal may in this way be accommodated. The liver becomes hard, tense, and swollen, and other tissues become edematous. Owing to the transudation of fluid, the body becomes dropsical. The bladder is distended with urine, and the stomach and intestines become filled out with fluid. These factors prevent the blood pressure from rising much above the normal. After the injection the arterial and venous pressures return quickly to the normal, generally within an hour. Injection of saline solution differs from transfusion of blood in that in the former case the blood flow is accelerated. The solution injected must be isotonic with the blood of the animal, of the same temperature, and every precaution taken to prevent the entrance of air. When injection of salt solution is maintained for some time, the work of the heart is increased, and cardiac failure sometimes results. In the endeavor to avoid the latter it has been found that bloodletting rapidly reduces arterial pressure, but owing to a general paralysis of the vasomotor apparatus through overdistention, the animal is easily killed by the hemorrhage. One hundred and fifty per cent. of the normal quantity of blood of the animal is the maximal amount that can be injected without directly endangering the life of the animal.

Transfusion of blood is *dangerous* for two reasons:

1. Strange blood, even after defibrination, carries an excess of fibrin ferment liable to cause intravascular clotting.

2. The blood of one animal has a *globulicidal* action and *toxic* effect on the corpuscles of another. By globulicidal action is meant that property of the serum of an animal which causes it to destroy the red corpuscles of the blood of another, thereby rendering it laky. The white corpuscles may be destroyed as well. As an example it may be said that man's serum is globulicidal to rabbit's blood. Similarly the blood of one animal may be poisonous to that of another aside from its globulicidal action. Thus the injection of 10 c.c. of dog's serum will rapidly kill a rabbit. These properties are destroyed if the blood is heated to 60° F., and they may, as has been suggested, be the result of a protein substance—an *alexine*—which is present in small quantities in the blood of every animal.

Biological Reactions of Blood.—Our knowledge concerning the hemolytic and toxic actions of the sera of animals has undergone great advances during the last decade and a half. These advances had their starting point in the observations of Bordet. The serum of guinea-pigs has little or no effect, normally, on the red corpuscles of rabbit's blood. If, however, one injects some rabbit's blood under the skin of a guinea-pig daily, for five or six days, it will be found that the blood of this particular guinea-pig has acquired a strong hemolytic action toward the erythrocytes of rabbits. This method of producing *specific hemolysins* is designated as a process of immunizing and the serum thus obtained is known as immune serum. Hemolysis, by means of immune sera, is the combined action of at least two bodies. One is a new and specific substance developed as the consequence of the injection of foreign erythrocytes. It is known as the *immune body* or *amboceptor*. It is not destroyed by moderate heating. The other is a body normally present in guinea-pig serum, but capable of acting on rabbit erythrocytes only through the immune body. This second body is known as the *complement*, and it may be destroyed by heating to 55° C. If, therefore, immune serum of the guinea-pig is heated to 55° C. it loses the power of hemolyzing rabbit's corpuscles, but this property is restored by adding a minute amount of the rabbit's own normal serum which supplies

the needed complement. The amboceptor, from this point of view, has a double specific combining power—on the one hand with the erythrocyte and on the other with the complement.

Generally, the serum of any animal is more or less hemolytic with respect to the corpuscles of an animal of another species, but in some normal sera this power is very prominent. This is the case in eel's serum. Here too the hemolysis is due to the interaction of two bodies. The strongest evidence against Bordet's conception of a sensitizing substance and in favor of the side-chain theory is that resulting from the study of cobra venom. Regarded as a hemolytic agent, cobra venom contains amboceptors only. If it be mixed with thoroughly washed goat erythrocytes, which contain no endocomplement, no hemolysis results until some complement (normal serum) be added also. If, however, snake venom and complement be mixed together so that there is a large excess of amboceptors in the mixture and then added to blood, then the erythrocytes will not undergo hemolysis. This is due to the *deviation of the complement,* all the complement available for the activation of the erythrocyte-amboceptor compound having become united with those amboceptors which are floating free and are not anchored to the erythrocytes. Such a result cannot be explained on Bordet's theory. Furthermore, in the case of snake venom it has been found that the complement which unites with the venom amboceptor is the well-known simple substance lecithin. If a chloroform solution of lecithin be shaken for two hours with cobra venom, a chemical compound, cobra lecithin, is formed which is actively hemolytic toward ox erythrocytes.

Side-chain Theory.—The theory which has won greater acceptance than Bordet's is the side-chain theory of Ehrlich and Morgenroth. It is most easily understood by considering the simplest case, that of antitoxin formation. If a bouillon culture of diphtheria bacillus be filtered through a Pasteur-Chamberland filter, the filtrate will contain diphtheria toxin, and will, if injected into susceptible animals, cause death. If, however, the toxin be injected at intervals of a few days apart, at first in sub-lethal doses, the animal will become immune. The serum of such an immune animal, if injected into a normal

animal, will protect the latter from subsequent injections of diphtheria toxin. Something has been developed in the blood of the immunized animal which can neutralize the toxin. This is called antitoxin. To explain the production of anti-toxin, the side-chain theory supposes that the biogen of the animal tissues consists of a central nucleus or functionating centre, attached to which are innumerable arms or side chains which are of various combining powers at their free ends. These side chains are concerned, physiologically, in the absorption of food molecules, which must, therefore, be likewise provided with side chains of definite combining powers. It is only by becoming locked to the functionating centre of a cell, by means of side chains, that food molecules can be incorporated with the protoplasm of the cell and its potential energy made available to the tissues.

A molecule of toxin possesses besides the actually toxic portion, known as the toxophoric group, a combining side chain known as the haptophoric group, and if it happens that the latter fits one of the side chains of the tissue cells, then will the toxin unite with the cell and produce the symptoms of the disease. In order to explain how the repeated injection of toxin in increasing dosage leads to the production of anti-toxin it is imagined that the union of tissue side chains with toxin molecules leads to an overproduction of similar side chains which are thrown off from the cells producing them and which float free in the blood. This assumption is based upon an observation of Weigert's, who showed that when a tissue is injured the organism not only makes good the defect, but reproduces the lost part in overexcess. The liberated side chains are the antitoxin. Side chains of the kind just considered are relatively simple, possessing but one combining group. They are known as receptors of the first order. In the case of hemolytic actions the disrupted biogen receptors are more complex, inasmuch as there is formed, not merely an inactive body as in the reactions between toxin and anti-toxin, but a new compound provided with combining groups not only for the erythrocyte but for the complement as well, for the latter produces the actual lysogenic effect. These are receptors of the third order.

Receptors of the second order are to be found in those bodies

responsible for the *agglutination* of red corpuscles. This is a phenomenon going hand in hand with hemolysis, but due to an entirely different agency. Bordet first observed that the serum of an animal which has been gradually injected with the blood of a second has the power of producing an immediate clumping of the corpuscles of the second animal when added to a portion of the latter's blood. The receptor which produces the clumping is supposed to be furnished at one end with a functionating or agglutinophoric group, the other end being a haptophoric group. When agglutination occurs, the latter is supposed to be anchored to a suitable receptor of the erythrocyte, so that the agglutinophoric group is enabled to produce some unknown change in the cells which causes them to clump together. The essential difference between receptors of the third order and those of the second order is that, in the former, the complementophilic group is replaced by a zymophoric or acting group, which does not require to become combined with complements before it can act.

Not only toxins and erythrocytes, but also proteins, can, when injected into an animal, lead to the production of specific bodies with which they react. When proteins are injected the reaction leads to a precipitation of the protein, and the bodies responsible for this are known as *precipitins*. The mechanism involved in the production of precipitins is identical with that involved in the production of agglutinins, *i. e.*, receptors of the second class are regenerated in overexcess.

According to the well-known theory of Metchnikoff, leukocytes, as a result of their power of phagocytosis, ingest invading bacteria and render them innocuous unless the bacteria be of such virulence as to poison the leukocytes. It has recently been discovered that there are certain substances in normal serum which act upon bacteria in such a way as to render them susceptible of being taken up by leukocytes. These substances are known as *opsonins*. By heating normal serum to 65° C. for fifteen minutes its opsonin is destroyed and it is then no longer capable of sensitizing bacteria toward leukocytes. The opsonin probably possesses a haptophoric group, by means of which it unites with the bacterium, and an activating group, whereby it produces some chemical or other change in the leukocyte which stimulates the latter to absorb the

bacterium. The relation is very much like that which holds in the complement, and this analogy is sustained by the same reaction of opsonins to heat.

QUESTIONS ON CHAPTER V

How does excessive hemorrhage affect man?

What is the function of the blood?

What is the total quantity in the body of man?

How does the quantity vary?

How is the total quantity of an animal estimated?

How is the blood distributed in the body?

What are the components of the blood?

What is the cause of the difference in color in arterial and venous blood?

What makes the blood opaque?

What is laky blood?

Give the physical and chemical properties of blood.

Discuss the chemical reaction of the blood.

What is meant by the titration alkalinity of the blood?

Discuss the corpuscles of the blood.

What is hemoglobin? How is it held in the corpuscle?

What is hemochromogen?

What is the total area which the red corpuscles expose to the action of the air?

Discuss some of the compounds formed by hemoglobin and various gases.

Explain why illuminating gas is dangerous when inhaled.

What is the percentage of iron in hemoglobin?

Describe the crystals of hemoglobin and their manner of preparation.

What are hemin crystals? How prepared? Of what importance are they?

Discuss the identification of human blood stains.

Discuss the absorption spectra of oxyhemoglobin and of reduced hemoglobin.

What facts indicate that red corpuscles remain in the vessels but a limited time?

What is hematopoiesis?

Where are red corpuscles formed? Describe the process.

How are the white blood cells classified?

What is diapedesis?

What is the function of leukocytes?

Discuss the blood plates.

Describe the plasma of the blood.

By what methods may plasma be obtained free from corpuscles?

Explain the effect of the injection of peptones into the blood of an animal.

Why do oxalate solutions affect coagulation?

What are the chemical constituents of plasma?

Give the percentage of serum albumin in the blood of man. How is it separated from the globulins?

What facts indicate that there is more than one kind of serum albumin.

What is the percentage of serum globulin in the blood? Give its probable source. How separable into different kinds of globulin?

What is the percentage of fibrinogen in the blood?

What substances are included under extractives?

What peculiarity in the distribution of salts in the corpuscles and in the plasma?

Describe the process of clotting.

How is the buffy coat produced?

Give the chemistry of clotting.

How is fibrin ferment obtained?

How has it been shown that fibrin ferment is normally not present in the blood?

Give proof as to the origin of the fibrin ferment.

How may intravascular clotting be produced?

Explain the "negative phase" produced by the injection of ferment into the vessels of an animal.

What experiment shows that the epithelial lining of the vessels normally prevents clotting of the blood?

How much blood may be lost without fatal results?

Why is the injection of sodium chloride solution beneficial after severe hemorrhage?

Why is the transfusion of blood dangerous?

What is meant by the globulicidal and toxic actions of the blood?

What is defibrinated blood?

What is the reason for the belief that two bodies are concerned in hemolysis by immune serum?

What evidence is there against Bordet's conception of a sensitizing substance in the hemolytic action of serum?

Give a brief exposition of Ehrlich's side-chain theory.

Differentiate between receptors of the first, second, and third order.

Explain the formation of antitoxin.

What are agglutinins, precipitins, and opsonins?

What is Metchnikoff's theory of phagocytosis?

CHAPTER VI

CIRCULATION

The Heart.—The blood is forced through the vessels that contain it mainly by the rhythmical contractions of the heart. Its path, in general, is as follows: Beginning with its exit from the left ventricle, it passes into the aorta, and through its various branches is rapidly taken into the systemic capillaries of all portions of the body. From the capillaries it is passed into the veins, which lead it back to the right auricle, through which it passes to the right ventricle. The latter, in turn, forces it through the arteries, capillaries, and veins of the pulmonary system to the left auricle, and then to the left ventricle, thus reaching its starting point. That portion of the blood which happens to pass into the capillaries of the stomach, intestines, spleen, or pancreas necessarily circulates through a second set of capillaries which are found in the liver, giving rise to what is known as the portal circulation. The kidney exhibits a somewhat similar arrangement.

Every particle of blood follows a path which, no matter how deviating it may be, finally returns into itself. The blood, moreover, is flowing always in a certain *definite direction.* This is the meaning of the expression *"circulation of the blood."* The left side of the heart forces the blood through the systemic vessels, while the right side forces it through the vessels of the lungs. It is thus possible for the blood to carry the foodstuffs absorbed from the intestines and those brought to it by the thoracic duct, as well as the oxygen which is absorbed in the lungs, to all the cells of the body. In addition it carries the waste products of the cells, in order that they may be removed by the proper excretory organs.

The energy of the contractions of the heart is derived from the potential chemical energy of the foodstuffs, and is entirely converted into heat before it leaves the body. Each contrac-

tion is technically known as a *systole*, and each relaxation as a *diastole*. During the systoles of the ventricles, which occur simultaneously, the blood is forced into the arteries, because the cavity of the ventricles is diminished in size, and, as the auriculoventricular valves are closed, the blood must pass through the open semilunar valves. During diastole the semilunar valves are closed, preventing the regurgitation of the blood from the arteries, but the auriculoventricular valves are now open, so that the blood in the large veins and in the auricles can enter the ventricles.

The beat of the heart consists of a regular sequence of events known as the *cardiac cycle*. The systoles of the two auricles occur together, as do those of the ventricles, and the same is true of their diastoles. While the auricles are contracting they shrink in size, and at this time the ventricles swell. Then follow immediately the systoles of the ventricles, during which the ventricles diminish in size, the auricles swell, and the injected arteries grow larger and longer. During the succeeding diastoles of the ventricles both ventricles and auricles swell until the next contraction of the auricles swells the ventricles still more. These changes in the size of the heart are due entirely to the varying amounts of blood contained, and not to any variations in the bulk of the heart muscle. In the relaxed condition the heart walls are very soft and flaccid. Owing to this fact the changes of form that the heart undergoes are easily modified by gravity when the thorax is opened and the heart exposed, since it is then unsupported by the lungs, which normally have a dilating influence. In this condition in an animal lying on its back it is seen that during a contraction of the ventricle the long axis of the heart sweeps toward the median line, and also toward the head, so that the apex rises a little toward the observer. The heart twists so that the left ventricle moves nearer the breast, while the right turns toward the spine. There is no change of color in the ventricle, but the auricles being thin, show the blood within— the right, bluish; the left, bright red. As the auricles contract they become paler. A distinct pulse is present in the arteries. In the unopened chest it is probable that the ventricles become smaller in girth during systole, and that they are always approximately circular and not elliptical. The ventricles shorten

somewhat in length, but the apex does not leave the chest wall, because the injected arteries at the base of the heart lengthen and push the entire heart forward, thus fully compensating for the shortening of the ventricle. The apex of the heart as it contracts hardens, and protrudes the chest wall in the intercostal space of the fourth and fifth ribs, midway between the left margin of the sternum and a vertical line let fall from the left nipple. This constitutes the *impulse* or *apex beat*, and it coincides with the upstroke of the pulse. Around the protrusion caused by the apex beat the soft parts of the chest wall are drawn in slightly, which is due to the fact that the heart becomes smaller at that time, and is, therefore, in contact with the chest wall over a smaller area. This drawing in is called the *negative impulse*.

Heart Sounds.—The heart during each cycle produces three sounds. The first, low pitched and muffled, coincides with the systoles of the ventricles, and is therefore heard when the apex beat is felt. The second sound is shorter, higher, and clearer than the other, and follows after a scarcely appreciable interval. It coincides with the early part of the diastole of the ventricle. After the second sound there is a period of silence, which is coincident with the latter portion of the diastole of the ventricle and the systole of the auricles. It has been proved that the second sound is due to the closure of the semilunar valves of the pulmonary artery and the aorta. When these are experimentally rendered incompetent, the second sound disappears and is replaced by a murmur. The first sound is believed to be due to the combined action of the closure of the tricuspid and mitral valves, and by the muscle sound produced by the ventricles in contracting. The first sound is heard best over the apex of the heart. The closure of the tricuspid valve can be listened to best at the lower end of the sternum. The second sound is heard best at each side of the sternum, between the first and second ribs, being propagated upward along the great vessels to which the semilunar valves are attached.

The third heart sound, heard in certain individuals, occurs about 0.13 second after the beginning of the second sound. It is best listened for over the apex of the heart. It is described as being softer and lower in pitch than the second sound and

is most likely due to a vibration of the auriculoventricular valves, early in diastole, when the inflow of blood from the auricles distends the ventricles sharply and suddenly, momentarily throwing the valves into a position of closure.

The average rate of heart beat in an adult man is about 72 a minute, and is somewhat faster in women. It varies, however, so that in some individuals it may be 40 or 100 a minute. Shortly before and after birth it averages from 120 to 140. During extreme age its frequency is increased. It is influenced by many conditions of bodily health and environment, such as sleep, position, temperature, meals, and emotions. Exercise may increase it to 200 or more.

The auricular systole is rapid, and forces the blood into the still quiescent ventricles. On completion of the auricular systole the auricles expand and remain quiet during the systole of the ventricles, which begins the moment the auricles cease contracting. The ventricular systole is more forcible than that of the auricles, and is sustained for a greater length of time. During ventricular systole the blood is forced into the arteries. At the close of the ventricular systole the ventricles dilate. The auricles do not take up the work again at once, but there is a period during which the entire heart is in repose. After this a new cycle is begun. If we assume the average number of heart beats to be 72 a minute, each cardiac cycle occupies 0.8 of a second. The contraction of the auricles lasts 0.1 of a second; that of the ventricles, 0.3 of a second; and the repose of the entire heart, 0.4 of a second. If the heart rate be increased, the ventricular systole remains about 0.3 of a second, and the increase in rate is made mainly at the expense of the time occupied by the diastole.

It is the function of the heart to force the blood in one direction only, and this is effected by means of the *valves*. As the ventricle fills, the auriculoventricular valves are floated up from the sides of the ventricle in such a manner that their edges are brought into contact. As the ventricle contracts more forcibly, pressure is brought upon the valves, so that not only are the edges in contact, but also portions of the surfaces of the cusps. These valves are of considerable area, and are held in position by the *chordæ tendinæ*, which arise from the *papillary muscles*, so that eversion of the valve into

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the auricle is impossible. The semilunar valves form a guard against the return of the blood to the ventricle at the pulmonary and aortic openings. These valves are forced open during the ventricular contraction by the blood which passes through them to distend the elastic walls of the large arteries. The pressure of the blood under the elastic recoil is sufficient to throw the cusps of the valves into action. The *corpora Arantii* are useful in making a perfect closure of the valve, although not absolutely essential. A part of the weight of this pressure is borne by the thick ventricular wall, which forms a ring from the outer edge of which the arteries spring, while the valves are attached to the inner edge.

Venous Pulse.—Under some circumstances the tricuspid valve does not entirely close, but allows a certain amount of regurgitation of blood. This occurs in conditions of disease or of violent exercise, when the lung capillaries are overcharged with blood. The leakage of the valve is conservative, and relieves the pressure upon the delicate capillaries of the pulmonary system. A pulsation in the jugular vein, in which the chief elevation is synchronous with the ventricular systole, indicates such a regurgitation. It must not be confused with a communicated venous pulse due simply to the proximity of some large artery; nor with a venous pulse due to a transmission of the arterial pulse through widened arterioles and capillaries; nor with a venous pulse in the jugular which depends upon variations of pressure in the auricle. The latter kind of venous pulse is of the greatest importance in an analysis of cardiac events. It manifests three distinct elevations or positive waves, separated by three depressions or negative waves. The first elevation corresponds to the systole of the auricle. The second is synchronous with the ventricular systole, and due, perhaps, to a sudden bulging of the auriculoventricular valve into the auricle. The cause of the third positive wave is not so clear. It is said to be due to the inflow of the venous blood. Its irregularity is occasioned by the muscular relaxation of the ventricle, and the return, therefore, of the base of the ventricle to its diastolic position. The auriculoventricular valve opens immediately afterward and the accumulated blood in the auricle passes into the ventricle causing a sudden fall of pressure in auricle and vein.

Work of Heart.—During each cycle of the heart there is ejected from the ventricles a quantity of blood known as the *contraction* or *pulse volume.* It varies in the same heart at different times, but on an average must be equal for both ventricles, and must also equal the amount that enters the systemic or pulmonary capillaries during the entire cycle. The amount may be roughly measured by introducing a modified stromuhr between the origins of the coronary arteries and of the innominates. It may also be measured by enclosing the heart in a plethysmograph. It has been estimated for man as being from 50 to 100 c.c. If its weight is taken at 100 grams and the blood in an average man weighs about 5300 grams, it is seen that *the pulse volume is equal to about one fifty-third of the entire blood, so that all the blood of a person passes through the heart in less than a minute.* Each pulse volume is injected into the arteries against considerable resistance, so that the ventricle performs work. The *amount of work* may be calculated by multiplying the weight of the pulse volume into the force exerted by the ventricles. The latter is equal to the pressure under which the pulse volume is expelled. This pressure may be measured in animals by introducing a tube through the external jugular into the ventricle, and connecting with a mercury manometer provided with a valve, so that the maximum pressure may be recorded. The left ventricle exerts more than twice as much power as the right. The exact intraventricular pressure in man has not been determined. It has been estimated as being equal to 0.150 meter of Hg on the left side and to 0.06 meter Hg on the right side. Employing the formula w = pr, and making suitable corrections by multiplying by 13.6, thus reducing the mercury column to an equivalent column of blood, it follows that the sum of the work performed by both ventricles is equal to 285.6 grammeters. To this must be added the energy represented by the velocity of the mass ejected into the large bloodvessels leaving the heart. Placing this velocity at 0.5 meter for both aorta and pulmonary artery, the energy represented in mechanical work is estimated from the formula $\frac{pv^2}{2g}$ in which p represents the weight of the mass moved, v the velocity of its movement, and g, the accelerating force of gravity. This gives 2.56 grammeters

for both ventricles making the total work of the heart equal to 288 grammeters of work. Practically all the energy of the heart's contractions is converted into heat by the friction of the blood in the vessels.

By the employment of maximum and minimum manometers it has been ascertained upon a dog in one case that the maximum pressure in the ventricle rose as high as 234 mm. Hg, while that in the aorta reached 212 mm. Hg. The minimum of the left ventricle was minus 38 mm. Hg, while that of the aorta did not get lower than 120 mm. Hg. These values vary, but their relations to one another may be taken as an example of what is true of both ventricles. It is seen that the pressure in the artery is always high, fluctuating but little, while that of the ventricles rises above the highest arterial pressure and falls much below. The pressure of the blood in the ventricle must overcome that within the artery to open the semilunar valves and force the blood into the artery. As the pressure falls in the ventricle the semilunar valves close as soon as it is less than that of the artery, and prevent regurgitation. When the pressure in the ventricles is at its lowest, the blood streams in from the large veins and from the auricles, because the pressure in the latter, although low, is higher than that in the ventricle.

Curves of endocardiac pressure which are obtained by inserting a hollow probe into the ventricles of the heart give a curve, characterized by a plateau, *i. e.*, the pressure instead of falling after reaching a maximum is sustained for some time (Fig. 2). The fluctuations of the plateau are due to oscillations produced by inertia. An endocardiac pressure curve very rarely shows any indication as to the *play of valves*. These must be obtained by carefully graduating two elastic manometers and connecting them with auricle and ventricle, or ventricle and aorta respectively. The relative pressures are given by the heights to which the recording levers rise, and thus the closure of the various valves may be ascertained. As long as the tricuspid or mitral valves are open the pressure in the ventricle is lower than that in the auricle, and the blood is entering from the veins. That in the arteries is shut out by the closed semilunar valves. This is called the *period of reception* of the blood. When the cuspid valves are shut the semilunar valves are open, and the

blood is being forced by the ventricle into the arteries. This is the *period of ejection*. There are two brief *periods of complete closure* of the ventricles, *i. e.*, when both cuspid and semilunar valves are closed. When the ventricle contracts upon its contained blood and thus raises the pressure, the cuspid valves close readily, but it takes some time for the pressure to become sufficiently high to open the semilunar valves. Similarly when the ventricle relaxes the high pressure in the arteries closes the semilunar valves immediately, but it takes some time for the pressure to fall low enough that the cuspid

Fig. 2
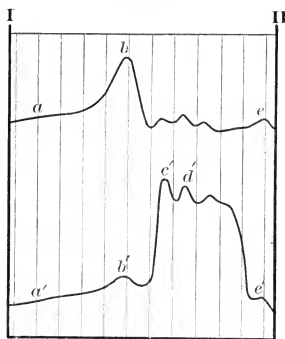
Simultaneous tracings from the right auricle and ventricle of the horse: *a, a'*, beginning of cardiac cycle; *b, b'*, rise of pressure due to auricular systole; *c'*, pressure due to ventricular systole; *d'*, oscillations due to inertia; *e, e'*, close of cardiac cycle. (After Chauveau and Marey.)

valves can open. During the ventricular diastole at the time when the cuspid valves are just opening the blood which has been accumulating in the auricles flows, and to some extent is drawn into the ventricles. This force of slight suction is due to the elastic fibers of the lung, which tend to open the ventricles and also to the elasticity of the heart muscle itself, especially of the auriculoventricular ring. The ventricles can maintain the circulation of the blood for a time at least, unaided by the auricles. The latter form a storehouse for the blood which accumulates during the ventricular systole. The pressure in them in the dog, for instance, seldom rises above

10 mm. Hg. They form therefore, but a feeble force pump which completes the filling of the ventricles. Their value in this respect becomes important when the heart rate increases, for then the ventricular pause is shortened and the auricles form an efficient *mechanism for quickly charging* the ventricles. The negative pressure of the auricles has been found to be as low as minus 10 mm. Hg. This is caused by the elasticity of the lung, which just at this moment is heightened because the contracting ventricle increases the negative pressure in the chest. The mouths of the great veins emptying into the auricles are unprovided with valves, but are rich in circular muscular fibers.

The systole of the heart begins in a small mass of embryonic tissue, *the sino-auricular node*, situated near the beginnings of the great veins. Owing to its more rapid rate of rhythmic discharge this part of the heart sets the pace for the remainder. Under special conditions other parts of the heart may initiate the rhythm. The diversity of opinion with reference to auto-maticity and rhythmical power of the heart residing in nervous or muscular structures has given rise to rival sets of theories— the neurogenic and myogenic respectively. In Limulus, at least, Carlson has definitely shown these powers to reside in a nervous apparatus but whether the same holds true for mammalia is still an open question.

The cause of the rhythmic movements of the heart lies within itself, since it can be severed from the central nervous system without necessarily destroying its activity.

A strip of muscle cut from the apex of a tortoise's heart in a zigzag manner, and suspended in a moist chamber, may beat as long as thirty hours with a slow rhythm. Very small microscopic pieces from the bulbus aortæ of the frog, which are probably devoid of nerve cells, contract rhythmically. Cu-rarized striated muscle placed in certain saline solutions will show a regular rhythm for hours. Many invertebrates have hearts that are not provided with nerve cells. *The heart of the embryo beats before the nerves have grown into it.*

The cardiac contraction is preceded by a change of electrical potential, which sweeps over it in the form of a wave. Both normally take the same course, beginning at the great veins and spreading rapidly over the auricles, then a short pause,

after which they spread over the ventricles. At times the contraction may originate in the ventricle. Thus by drawing a tight ligature about the heart at the junction of the auricles and ventricles, the rhythm of the heart is disturbed and the ventricle beats with an independent slower rhythm. If the *electrical changes* of the beating heart are investigated, it is found that the base becomes negative before the apex, and that this condition of negative potential passes along in the form of a wave to the apex. Its speed has been found to average at least 50 mm. a second. The *latent period* of frog's heart muscle is about 0.08 of a second, but the change of potential takes place instantly after the application of the stimulus. The *excitation wave* can be made to pass over the heart in any direction, and the speed with which it travels indicates that it passes through muscle and not through nerve. The duration of the pause or block in the frog's heart has been found to be from 0.15 to 0.30 of a second. The speed of the excitation wave in embryonic muscle (3 to 11 meters a second) makes it plausible that in the heart the block is due to the fact that the excitation wave is transmitted through embryonic muscle fibers that exist between the auricle and ventricle. The connection between auricles and ventricles in mammals is made by a strand known as the *atrioventricular bundle*. It begins in the auricular septum as a definite bundle. Branches on the auricular side may be traced back as far as the great veins or into the coronary sinus. This bundle passes down to the ventricular septum where it divides, one limb passing into the right ventricle beneath the endocardium and one into the left ventricle. Within the ventricles each limb forms a branching system long known as the Purkinje cells. There is no doubt that it conducts the wave of contraction or excitation from auricles to ventricles, for compression of the band produces a block. With a certain degree of pressure the ventricles beat only once for each two beats of the auricle. With greater pressure only once for each three or more auricular beats until finally, the ventricle beats independently of the auricles with a slower rhythm. In disease such an interference is not uncommon and is known as Stokes-Adams disease. The ventricle then beats about thirty per minute and this rate is but little influenced by events, like mental excitement, which normally

Fig. 3
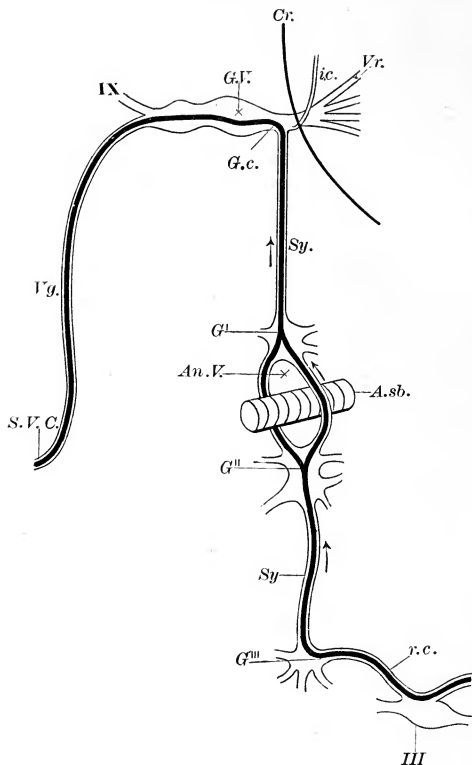
Diagrammatic representation of the course of cardiac augmentor fibers in the frog (Foster): *V.r.*, roots of vagus (and ninth) nerve; *G.V.*, ganglion of same; *Cr.*, line of cranial wall; *Vg.*, vagus trunk; *IX*, ninth, glosso-pharyngeal nerve; *S.V.C.*, superior vena cava; *Sy.*, sympathetic nerve in neck; *G.c.*, junction of sympathetic ganglion with vagus ganglion sending *i.c.*, intracranial fibers, passing to Gasserian ganglion. The rest of the fibers pass along the vagus trunk. G^1, splanchnic ganglion connected with the first spinal nerve; G^{11}, splanchnic ganglion of the second spinal nerve; *An.V.*, annulus of Vieussens; *A.sb.*, subclavian artery; G^{111}, splanchnic ganglion of the third spinal nerve; *III*, third spinal nerve; *r.c.*, ramus communicans.

The course of the augmentor fibers is shown by the thick black line. They may be traced from the spinal cord by the anterior root of the third spinal nerve, through the ramus communicans to the corresponding splanchnic ganglion G^{111}, and thence by the second ganglion G^{11}, the annulus of Vieussens, and the first ganglion G^1, to the cervical sympathetic *Sy*, and so by the vagus trunk to the superior vena cava *S.V.C.*

FIG. 4

Diagrammatic representation of the cardial inhibitory and augmentor fibers in the dog. The upper portion of the figure represents the inhibitory, the lower the augmentor fibers (Foster): r.Vg., roots of the vagus; r.Sp. Ac., roots of spinal accessory, both drawn very diagrammatically; G.J., ganglion jugulare; G Tr. VG., ganglion trunci vagi; Sp.Ac., spinal accessory trunk; ext.Sp.Ac., external spinal accessory; I.Sp.Ac., internal spinal accessory; V.g., trunk of vagus nerve; n.c., branches going to heart; C.Sy., cervical sympathetic; G.C., lower cervical ganglion; A.sb., subclavian artery; An V., annulus of Vieussens; G.St., (Th.¹), ganglion stellatum, or first thoracic ganglion; G.Th.², G.Th.³, G.Th.⁴, second, third, and fourth thoracic ganglia; D.II, D.III, D.IV, D.V, second, third, fourth, and fifth thoracic spinal nerves; r.c., ramus communicans; n.c., nerves (cardiac) passing to heart (superior vena cava) from cervical ganglion and from the annulus of Vieussens.

The inhibitory fibers, shown by black line, run in the upper (medullary roots) of the spinal accessory, by the internal branch of the spinal accessory, past the ganglion trunci vagi, along the trunk of the vagus, and so by branches to the superior vena cava and the heart.

The augmentor fibers, also shown by black line, pass from the spinal cord by the anterior roots of the second and third thoracic nerves (possibly also from fourth and fifth as indicated by broken black line), pass the second and first (stellate) thoracic ganglia by the annulus of Vieussens to the lower cervical ganglion, from whence, as also from the annulus itself, they pass along the cardiac nerves to the superior vena cava.
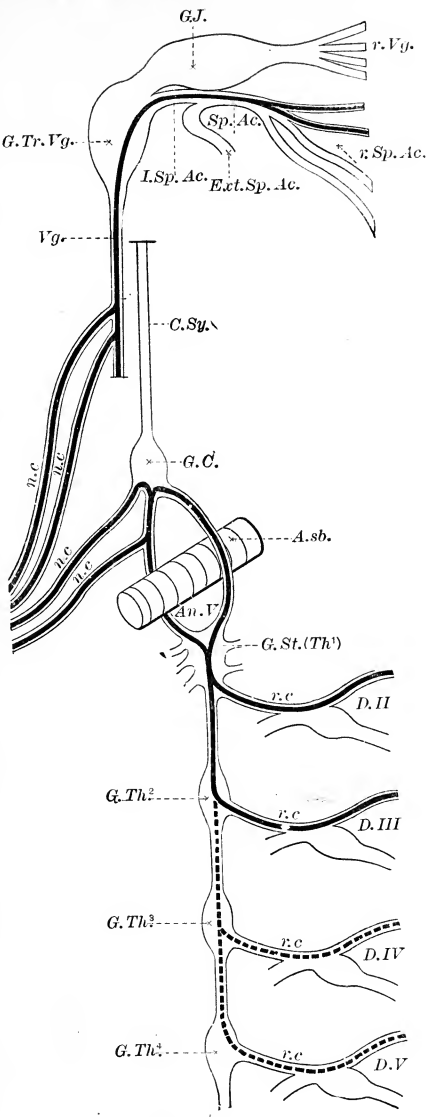
causes a marked increase in pulse rate. In some cases lesions have been found in the atrioventricular bundle but in others a cardio-inhibitory excitation of an already permanently diminished conductivity of the bundle is responsible. It is found that when a heart is subjected to a series of stimuli it will respond regularly when the rate is slow, but when it becomes too rapid, the stimuli will not all be able to call forth a response. The heart muscle loses its irritability during a part of its systole, and regains it during the remainder of the systole and the following diastole. During a part of the cardiac cycle, therefore, it is refractory to stimuli. A stimulus falling within the *refractory period* is without effect. A stimulus falling within the non-refractory period calls out a contraction, but does not disturb the rhythm of the heart, because it is followed by a pause of extra length. This is called the *compensatory pause.* The first systole after an extra contraction and a compensatory pause is of marked strength.

The **nerves of the heart** are branches of the *vagus* and the *sympathetic.* Some of the fibers of the vagus which are derived from the spinal accessory terminate in end baskets which surround sympathetic ganglion cells whose axis cylinder processes end on the muscle fibers. Other fibers of the vagus end in end brushes in the pericardium and endocardium. Fibers of the sympathetic system arise from cells in the cord and pass out through the white rami, ending in the inferior cervical and stellate ganglia on cells whose axis cylinder processes in turn pass either directly to the heart muscle or to a third neuron lying in the heart.

Stimulation of the vagus fibers along any portion of their path from the medulla to the heart inhibits the heart's action. The effect is not immediate, but follows a latent period which extends over a beat or two. The *inhibition* manifests itself at first by a lengthening of the duration of the diastole without any change in the systole. A stronger stimulation lengthens the systole also, and may stop the beat of the heart altogether. Inhibition is further shown by a lessening of the force of the contraction; by an increase of pressure in the heart during diastole; by an increase in the amount of residual blood; by a decrease in the input and output of the ventricle, and by diminished ventricular tonus. It may further be said that

during vagus excitation the propagation of the cardiac excitation is more difficult. A demarcation current derived from a portion of the auricle is increased by vagus excitation, although the auricle shows no visible change of form. The heart cannot be continuously inhibited by prolonged stimulation. It escapes from the influence of the vagus and resumes its former rhythm with perhaps increased force. Immediate stimulation of the second vagus after the heart has escaped from the influence of the first is without effect, making it probable that both nerves act upon the same mechanism in the heart.

Stimulation of the sympathetic or augmentor fibers causes an increase in the rate of the heart beat from 7 to 70 per cent., the amount of increase depending upon the heart's rate before stimulation. A long excitation produces no greater acceleration than a short one. The force of the beat, the pulse volume, and the speed of the excitation wave are all increased. The latent period is usually a long one, extending from two to ten seconds. The acceleration may continue for several minutes after the excitation has ceased. It has been found that pressure brought to bear upon the human heart where a defect in the chest wall makes it accessible can be felt by the subject, and direct stimulation of the surface of the heart in animals may cause movements of the limbs. The latter event is absent when the vagi are cut, so that it is thought the vagus carries afferent fibers to the brain. Stimulation of the central end of the cut vagus when the other is intact slows the heart rate. This effect disappears when both vagi are cut.

The *depressor* is a nerve whose fibers pass from the heart to the central nervous system. Section and stimulation of the peripheral end cause no appreciable change. Stimulation of the central end causes a general fall of blood pressure to one-half or one-third its former height, and lessens also the pulse rate. Both are restored after stimulation ceases. When both vagi are cut there is a fall of blood pressure upon stimulation of the depressor, but no change in the pulse rate. This shows that the impulses from the depressor may spread to the cardio-inhibitory centre and through the vagi slow the heart. It shows, moreover, that the fall in pressure is not dependent upon the vagi. Section of the *splanchnic nerve* causes dilatation of the abdominal vessels and a fall of the

general blood pressure. If, now, the depressor is stimulated little effect is produced, because the blood pressure is already so low that little more fall can be brought about. If, however, the general pressure is raised by stimulation of the splanchnic or by the injection of saline solution, then stimulation of the depressor produces a typical fall. This nerve is normally made active by stimuli arising from the endocardium of the heart when that organ is overcharged with blood. The impulses are conveyed to the vasomotor centre, which causes a dilatation of the arterioles all over the body. Unlike the vagi, the depressor is active only at times.

In general it may be said that weak stimulation of any *sensory nerve* like the sciatic produces augmentor effects, while a strong stimulation produces inhibitory effects. Stimulation of the central end of the abdominal sympathetic produces through the vagi a reflex inhibition of the heart. *Dilatation* of the *stomach* has experimentally been shown to *inhibit* the *heart*.

The *cardio-inhibitory* centre is situated in the bulb at the level of a mass of cells known as the nucleus of origin of the tenth nerve. The centre is probably always in action, since section of the vagi, which removes the influence of the centre, is followed by an increase in the rate of the heart beat. The continuous activity of the centre is due to a stream of impulses that come from all portions of the body. After cutting off most of these by dividing the spinal cord near the bulb, section of the vagi no longer increases the heart rate. The *augmentor centre* is situated somewhere in the bulb and is also continuously active. This is shown by sectioning the vagi and then extirpating the inferior cervical and first thoracic ganglia on both sides, which causes a slowing of the heart. Dividing the cord in the cervical region after the vagi have been cut has the same effect. Inhibition of the heart through the vagi is more easily obtained when the augmentor fibers have been severed. Whenever sensory nerves are stimulated, producing an accelerated heart beat, it is probable that both the augmentors and the cardio-inhibitory centres are stimulated, but the first more strongly, so that its effects prevail. There are a few cases on record where the heart centres in the medulla were apparently influenced by voluntary impulses from the cerebral cortex, but these are extremely unusual.

The heart of the higher animals has a distinct arterial and venous system, upon which its nourishment depends. The arteries in the human heart each supply a given area of the muscle, not invading the area of its neighbors, and no collateral circulation can be established between them. If, therefore, an artery is plugged by embolism or thrombosis, the part of the heart wall that it supplies dies, becoming dull white or faintly yellow in color, granular in cross-section, and is soon replaced by connective tissue. Such an area is known as an *infarct*. The result of closure of the arteries of the heart depends upon the size of the vessel operated upon. Sometimes no effect is produced, or the ventricles may stop beating and fall into fluttering, twitching movements known as *fibrillary* contractions. The auricles will, perhaps, continue beating for a short time. As the arrest of the heart draws near the force of the ventricular beat becomes irregular, but the pressure in the heart gradually lessens during systole and becomes greater during diastole. The cause of the arrest is not the mechanical injury done to the heart, but the sudden anemia produced. Anemia brought about by hemorrhage produces a different series of symptoms because the heart works against decreasing resistance in the arteries, which is not the case when a branch of the coronary artery is ligated, for then the peripheral resistance continues to be high. Closure of the coronary veins produces fibrillary contractions in a rabbit in from fifteen to twenty minutes, but is without effect upon the dog, owing to the fact that some of the blood passes into the cavities of the heart through the *venæ Thebesii*, and is sufficient in amount to maintain the nutrition of the heart.

The contractions of the heart favor the passage of the blood through the coronary arteries in two ways:

1. By the pressure produced in the aorta.

2. By rhythmically compressing the walls of the bloodvessels in the heart muscle.

It has been found that the volume of the blood passing through the coronary circulation, unless it varies very much, does not influence the rate of the beat, but does modify the force of the contraction.

The various constituents of the complex fluid, blood, have different values in maintaining the activity of the heart. This

has been investigated by the use of nutrient solutions of definitely known composition. The results obtained are briefly as follows: Nutrient fluids for the heart must be alkaline in reaction. Sodium carbonate is the alkali generally used. It has no specific action, but neutralizes the carbon dioxide and acids formed by the activity of the heart muscle. Sodium chloride must be present of a strength isotonic with the blood of the animal. Some calcium salt to prevent the diffusion of calcium out of the muscle fibers is essential to continued contractions. Calcium salts tend to produce prolonged tonic contractions, and this effect is neutralized by the addition of potassium salts. When calcium salts are removed from a solution by the addition of oxalate compounds, the heart ceases to beat, but spontaneous contractions return when calcium is again added. A well-known nutrient solution is *Ringer's*, which is a mixture of 100 c.c. of a 0.6 per cent. sodium chloride solution saturated with tribasic calcium phosphate and 2 c.c. of a 1 per cent. solution of potassium chloride. Oxygen is essential to the prolonged activity of the heart. Carbon dioxide is injurious when present in large quantities. A heart poisoned with the latter substance shows an irregular series of contractions. It has not been satisfactorily demonstrated that organic substances are immediately necessary to the rhythmic activity of the heart.

Arteries, Capillaries, and Veins.—The continuously high pressure that exists in the aorta causes the blood to move to points of lower pressure, and it is thus kept in constant movement from the arteries through the capillaries to the veins, and so back to the heart, where, by the action of this organ it is again transferred into the artery and put under high pressure. *Blood pressure* is usually measured by an instrument called a *mercury manometer*. It consists of a U-shaped glass tube, the bend of which is filled with mercury. One limb of the tube, filled with an anticoagulation fluid, is put in connection with the bloodvessel of the animal, while the surface of the mercury in the other limb carries a small float to which is attached a delicate pen that bears against a horizontally moving surface. Such an arrangement is a *kymograph*. Variations of the blood pressure within the vessel are transmitted through the fluids to the mercury, which moves up

and down, carrying the float and pen with it, and are thus recorded. By this method it is found that the blood in an artery exhibits at least two regularly recurring changes of pressure, which take the form of smaller waves superimposed upon larger ones. The latter are due to respiratory movements, while the former are due to heart beats (Fig. 5). The *mean blood pressure* is the average pressure during any arbitrarily chosen length of time. This in man is about 150 mm. Hg or more in the aorta; from 10 to 70 mm. Hg in the capillaries. In the external jugular and in the veins near the heart the pressure becomes negative. From the aorta through the capillaries and veins back to the heart there is a continuous decline in pressure.

FIG. 5
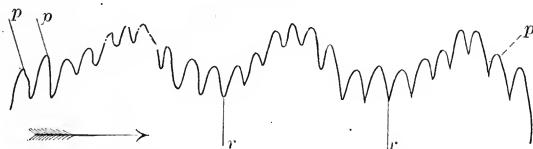
Tracing of arterial pressure with a mercury manometer (Foster). The smaller curves, *p p*, are the pulse curves. The space from *r* to *r* embraces a respiratory undulation. The tracing is taken from a dog, and the irregularities visible in it are those frequently met with in this animal.

The cause of the high pressure in the aorta is the intermittent entrance into it of jets of blood, the resistance offered by the peripheral capillaries and the elasticity of the vessel walls. Each volume of blood forced into the aorta from the heart distends the wall of the vessel, which, through its elasticity, tends gradually to return to its normal size during every diastole of the heart. It is at all times, however, stretched, and therefore, always exerts a pressure upon the blood within. Under normal conditions the amount of blood accommodated by the yielding artery during each systole is equal to the amount that passes from the arteries and to the capillaries during the diastole of the heart. Each increase of pressure caused by the heart beat is propagated in the form of a wave through the arterial system, and constitutes what is called the *pulse.*

The pressure in the capillaries and veins is caused by the same factors that are present in the aorta—power of the heart,

resistance of friction, and elasticity of bloodvessel walls. But in the capillaries and veins their is no pulse and the pressure is low. The cause of the latter becomes obvious when it is taken into consideration that a part of the force of the heart has been lost in overcoming the friction of the bloodvessels. In addition, the friction which the blood has yet to overcome in its passage back to the heart is but a fraction of the total friction which it encountered at first. Diminished resistance ahead means lowered pressure. The blood in the capillaries has become pulseless, because the elasticity of the arteries displaces the blood in the capillaries at the same rate that the systole of the heart does.

There are *subsidiary forces* that assist the heart in propelling the blood. Among these may be mentioned the contractions of the skeletal muscles, the constant pull of the fibers of the lung, and the movements of respiration. The muscles, in contracting, press upon the veins moving the contained blood onward, since the valves prevent all back flow. The fibers of the lungs, through their elasticity, are constantly pulling upon the walls of the heart and the large veins, which tends to draw the blood into them. This effect is increased with each inspiration, and the blood then rushes in at a quicker rate; during the following expiration the blood flows more slowly again. There may in this way arise a distinct pulse in the large venous vessels of the chest, which may extend along the veins to the root of the neck. In this region, in deep respirations, there may be an intermittent flow of blood from a cut vein. The bleeding occurs during each expiration and ceases during each inspiration, when the blood is sucked past the wound and not pressed out of it. Owing to this reason air may be drawn into the vein, an event which causes immediate death. This region is, therefore, known as the *dangerous region.*

The Pulse.—By the term *arterial pulse* is meant the fluctuations of arterial pressure that correspond to the beats of the heart. The pulse is dependent upon:

1. The contractions of the heart.

2. Upon the resistance produced by the friction of the blood in the vessels.

3. Upon the elasticity of the bloodvessel walls. An abnormal change in either of the three will modify its character. An artery not only increases in its girth as the pulse wave sweeps over it, but also in its length, which can readily be seen when the vessel has a sinuous course. The increase in girth can be felt when the artery is pressed upon with the finger, and forms a constant means of diagnosis. The rate of the pulse wave is from 6 to 9 meters a second. As the blood moves on an average in the arteries only one-half a meter in the same time, it is clear that it is not the travelling of the blood that produces the pulse, but a wave of pressure. A number of terms describe the character of the pulse. In regard to its tension it may be:

Of high tension or of low tension.

Incompressible or compressible.

Hard or soft.

Very hard (wiry) or very soft (gaseous).

High tension is indicative of high blood pressure, which can be measured by a *sphygmomanometer*. In regard to its size the pulse may be:

Large or small.

Very large (bounding) or very small (thready).

A large pulse often indicates a low mean blood pressure. Finally, the pulse may be short or long. It is long when the upstroke takes place slowly.

While an experienced physician can appreciate slight variations in the character of the pulse, it is only by means of the graphic method that different kinds of pulse can be investigated successfully and records kept. The *sphygmograph* is an instrument which measures the succession of alternate dilatations and contractions of an artery, magnifying them, and registering them on a surface moving at a uniform rate by clockwork. The tracings show variations of the pulse too slight to be appreciated by the most experienced fingers. The record of a sphygmograph is called a *sphygmogram*. Each pulsation of the artery is seen to be made up of a sudden and direct upstroke and a gradual oscillating downstroke. The latter in typical tracings is made up of three waves, of which the middle one is the most pronounced, and is known as the *dicrotic wave*. When the dicrotic wave can be felt with the finger,

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the pulse is spoken of as a *dicrotic pulse.* This is apt to *accompany* a low *blood pressure. The dicrotic wave is caused by a sudden tension of the semilunar valves.*

The blood moves through the arteries in a series of pulses which grow less and less pronounced, until they are extinguished in the capillary district. Here the blood flows toward the veins with much friction, slowly and under comparatively low pressure. Instruments have been devised to measure rapid fluctuations of speed. They consist essentially of a needle, which is thrust through the wall of the vessel. The amount that is deflected from the perpendicular by the movement of the blood is read on a graduated semicircle which is placed under the free end of the needle. It has been ascertained that the blood in the large arteries flows at a rate of from 250 to over 500 mm. a second. The speed in the veins is somewhat slower. In the capillaries it has been measured directly under the microscope, and some physiologists have observed it in the retinal capillaries of their own eyes. It flows from 0.6 to 0.9 mm. a second. The speed and pressure of the blood rise and fall together in the arteries, but whereas the pressure falls continuously from arteries to veins, the speed falls from arteries to capillaries, but is increased again in the veins as it approaches the heart. The speed does not depend upon the pressure alone, but also upon the width of the blood path. Whenever a vessel divides, the cross-sectional area of its branches is greater than that of the vessel itself. The *collective sectional area* of the capillaries is several hundred times that of the aorta, while the latter is one-half that of the venæ cavæ. The blood then flows swiftly through the arteries to the capillaries, where it performs its functions and is returned almost as quickly to the heart by the veins. It has been estimated that the blood remains about 0.6 of a second in a capillary $\frac{1}{2}$ mm. long.

The **pulmonary circulation** differs in minor respects from the systemic. The total friction is less, in correspondence with which the right ventricular walls are far thinner than those of the left ventricle. Owing to the fact that the pulmonary system lies entirely within the thorax, it is subjected to the negative pressure which exists there, and the veins and arteries are opened by the elastic pull of the lungs. This tends to favor

the flow in the veins and to hinder it in the arteries. The flow in the latter, however, is not affected much on account of the thickness of the arterial walls, so that, on the whole, the negative pressure in the thorax, increased with each inspiration, helps the pulmonary circulation. The capillaries are situated so close to the surface that they are exposed to atmospheric pressure. Every expiration presses the blood out of them, and so again the flow is favored.

Vasomotor System.—The heart pumps the blood through all parts of the body, but the amount in any one portion depends upon the active dilatation or contraction of the vessels. That an artery may dilate was first shown by Bernard, who cut the cervical sympathetic of a rabbit on one side and found an increased redness of the skin of the ear and an elevation of the temperature of from four to six degrees, which persisted for months. If the peripheral end of the cut nerve is stimulated with a galvanic current, normal conditions are resumed, which last only as long as the stimulus is applied. The existence of *dilator nerves* is placed beyond doubt by the results obtained upon the chorda tympani of the submaxillary gland. Nerves that bring about a dilatation of bloodvessels are called *vasodilator nerves;* those that cause a constriction are called *vasoconstrictor nerves.* Both are present in the nerves of the sympathetic system, as well as in the cranial and spinal nerves. They also supply veins. The *portal vein*, for instance, may be made to contract by stimulation of the peripheral end of the cut splanchnic. The changes in the capacity of the bloodvessels may be studied by direct inspection in many cases, but often it is more satisfactory to place a manometer in a branch of the artery that supplies the portion of the animal under observation. The principle underlying this is that the pressure in an artery depends upon the resistance to be overcome in its distal capillaries. Another method of studying vasomotor phenomena is to enclose a portion within an airtight cylinder, which usually is filled with a liquid and is connected with a tambour. Changes in volume of the parts enclosed, due to variations in the amounts of blood, are transmitted to a tambour. Such an instrument is called a *plethysmograph*.

Vasoconstrictor and vasodilator nerves are usually found

in the same nerve trunk. Upon stimulation the effects of one may be entirely masked by the effects of the other, so that it becomes necessary to learn the differences between the two.

1. The vasoconstrictors are excited less easily than the vasodilators.

2. The after-effect of stimulation of the constrictors is shorter than that of the dilators.

3. Warming increases the excitability, and cooling decreases it, more in the constrictors than in the dilators.

4. The maximum effect of stimulation is reached more quickly in the constrictors than in the dilators.

5. The constrictors have a latent period of 1.5 seconds; that of the dilators is 3.5 seconds.

The Vasomotor Centre.—There is in the medulla on each side of the median line a group of cells lying in the region of the nucleus of the facial and of the superior olive. This is the situation of the *vasomotor centre.* It is bilateral, and occupies an area caudal to the corpora quadrigemina. When sections are made through successive levels of the bulb, the pressure of the blood begins to fall when a point is reached about 1 mm. caudal to the quadrigemina, and continues to fall until an area extending over the fourth millimeter has been reached. There is then no further fall. The centre continually sends impulses along fibers that extend to the nuclei of various cranial nerves, and also down the lateral columns of the cord to small cells situated at various levels in the anterior horn and lateral gray substances. From these cells axis cylinders pass out through the anterior roots of the cranial and spinal nerves and enter the sympathetic ganglia. Here cells, in turn, send out processes that end on the muscle fibers of the bloodvessels. *The evidence for the existence of subsidiary spinal centres is conclusive.* It has been found that in a dog whose cord is severed at the junction of the dorsal and lumbar regions mechanical stimulation of the skin of the abdomen and penis will cause erections. This is a vasomotor reflex due to dilatation of bloodvessels of the penis through the nervi erigentes. Again, section of the cord in the dorsal region of a dog is followed by a vasodilatation of the arteries of the hind limbs. If the animal continues to live, the limbs are in time restored to their normal condition. Destruction of the lumbar cord now brings

on a second dilatation. It must be assumed, therefore, that centres exist in the cord which normally are controlled by the bulbar centre, and that when severed from the latter will become gradually independent. There are, in addition to the vasomotor centres already mentioned, centres in the sympathetic ganglia. Destruction of both bulbar and spinal centres

FIG. 6
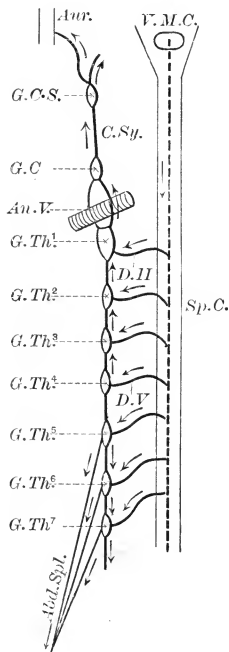
Diagram illustrating the paths of vasoconstrictor fibers along the cervical sympathetic and (part of) the abdominal splanchnic (Foster): *Aur.*, artery of ear; *G.C.S.*, superior cervical ganglion; *Abd.Spl.*, upper roots of and part of abdominal splanchnic nerve; *V.M.C.*, vasomotor centre in medulla; *C.Sy.*, cervical sympathetic; *G.C.*, lower cervical ganglion; *G.Th.*[1] to *G.Th.*[7], the thoracic ganglia, first to seventh both inclusive; *D.II* and *D.V*, respectively the second and fifth dorsal nerves; *An.V.*, annulus of Vieussens. The paths of the constrictor fibers are shown by the arrows. The dotted line in the spinal cord, *Sp.C.*, is to indicate the passage of constrictor impulses down the cord from the vasomotor centre in the medulla.

does not destroy arterial tone completely. For example, the lower portion of the spinal cord of a dog was removed for about 80 mm. The dilatation of the vessels of the hind limbs which followed was succeeded in time by a constriction, leaving the temperature of the limbs even cooler than normally.

Long oscillations in blood-pressure curves due to vaso-

motor changes are often called *Traube-Hering* waves. They indicate alterations in the tonus of the bloodvessels, and are caused by irradiations of impulses from other centres to the vasomotor centre. *Vasomotor reflexes* arise by impulses which come either from the bloodvessels or from the end organs of sensory nerves. In the latter case the dilatation affects not only the portion from which the impulses come, but also parts functionally related. Thus stimulation of the tongue causes dilatation of the vessels of the submaxillary gland. The fact that stimulation of the same nerve gives rise sometimes to a reflex dilatation instead of the more usual constriction, has given rise to the conception of special *pressor* and *depressor* fibers. The former constrict, the latter dilate. The cardiac depressor nerve is a good example. Its fibers form afferent paths from the heart and from the root of the aorta. If cut, and the peripheral end is stimulated, no result follows. If, however, the central end is stimulated, a fall of blood pressure occurs and also perhaps a slowing of the heart beat. The latter effect is due to a reflex stimulation of the cardio-inhibitory centre. The fall in blood pressure takes place because the nerve when stimulated inhibits the tonic activity of the vasoconstrictor centre. In this way the nerve plays an important regulatory role, for if the blood pressure rises above normal limits the endings of the nerve will be stimulated. Each heart beat, in fact, sends up the depressor nerve a nerve impulse which can be detected by a string galvanometer. It forms part of an important compensatory blood-pressure mechanism.

The chemical regulation of the caliber of bloodvessels has recently been emphasized. Acids, in slight concentration, like lactic or carbonic, produce a dilatation. They may serve as the cause of a local dilatation during functional activity, and thus provide the organ with more blood. On the other hand, the internal secretion of the adrenal gland and possibly also of the infundibular portion of the pituitary have a reverse effect. The distention of the arterioles by internal pressure may act as a mechanical stimulus and lead to an increased tone.

Circulation of Lymph.—Lymph is a pale, straw-colored liquid found in the extravascular spaces (and lymph vessels of the body), bathing every tissue element. It contains a

number of leukocytes; accidentally, red corpuscles and blood plates; after meals, fat globules. Lymph contains the proteins, the extractives, and the salts of blood. The last are in the same proportions as in blood; the proteins and especially the fibrinogen are present in lesser amounts. Lymph coagulates more slowly and less firmly than blood. During digestion there is a marked increase in fats in the lymph of the intestine, making it resemble milk, and it then becomes known as chyle. The lymph derives substances from three sources—from the blood, from the tissues, and from the villi of the intestines. The fluid which fills the interstices of the tissues is not in open communication with the lymph in the lymph capillaries. The latter, ramifying the tissues, end blindly in single-layered endothelial walls. From the capillaries the lymph is passed into definite lymphatic vessels which finally empty their contents into the bloodvessels at the junction of the subclavian and internal jugular veins.

The lymph, in moving from the tissue gaps and lymph capillaries to the veins, passes from a point of relatively high pressure to one of low pressure. The pressure in the lymph capillaries has been estimated at from 12 to 25 mm. Hg; in the thoracic duct, near its entrance into the veins, it is very near to zero, and often is negative. In some of the lower animals there are separate lymph hearts which act as force-pumps to drive the lymph on. In man such lymph hearts do not exist, but the movement is brought about by other factors:

1. By the continual formation of new lymph.

2. By the muscular movements of the body compressing the lymphatics, which force the lymph on in the proper direction, the reverse flow being prevented by valves. The chyle is aided in its flow by the action of the muscular fibers of the small intestine and also by the contractions of the villi. In the mouse the chyle has been seen to flow with the intermittent movements corresponding to the peristaltic waves. The contractility of the walls of the lymph vessels themselves probably aids the flow.

3. The thoracic aspiration of the chest on inspiration draws the lymph into the thoracic cavity in the same manner as it draws the venous blood. The movement of the lymph is, without doubt, irregular, but in the course of a day a con-

siderable amount is poured into the veins. A substance in solution injected into the blood can be detected at the mouth of the thoracic duct in from four to seven minutes. The lymphatic capillaries in different regions of the body have a different structure which is not optically recognizable but which gives them different physiological properties, so that they influence the character of the lymph formed, particularly in regard to the percentage of protein.

QUESTIONS ON CHAPTER VI

Give the path of the blood through the body.
Give the path of the blood through the portal system.
What is meant by "circulation of the blood"?
What function is fulfilled by the circulation?
Whence does the heart derive its energy?
Define systole and diastole.
By what means is the blood forced in one direction only?
What different events take place during a cardiac cycle?
To what are the changes in the size of the heart due?
What is the condition of the heart when relaxed?
What changes take place in the heart during systole when the thorax is open?
How are these changes modified in the unopened chest?
Give the changes of color of the heart during contraction.
Why does the heart not move from the chest wall during systole?
Where is the apex beat felt?
What is meant by "negative impulse"?
Describe the sounds of the heart.
With what portions of the cardiac cycle do they coincide?
What is the cause of the heart sounds?
Where can the sounds be best heard?
Discuss the rate of the heart beat.
Describe the character of the contractions of the auricle and ventricle.
Give the times involved by the various events of the cardiac cycle.
What changes take place in regard to the time occupied by the cardiac cycle events when the heart rate is quickened?
Describe the action of the valves during a heart beat.
Discuss the venous pulse.
What is the pulse volume?
How is the pulse volume obtained? What is its value?
How is the work of the heart calculated?
How are intraventricular pressures determined?
How much work does the heart do in a day?
What are the relative pressures in ventricle and aorta?
Discuss endocardiac pressure curves obtained from ventricle with different methods.
To what are the oscillations of the plateau due?
In what way may the times of closure and opening of the valves be ascertained on intracardiac pressure curves?
Define "period of reception" and "period of ejection."
Discuss periods of complete closure of the ventricles.
Can the ventricles alone maintain circulation?

What is the function of the auricles?

What variations in pressure are there in the auricles?

Discuss the entrance of the blood into the auricles from the veins.

Discuss the cause of the rhythmic activity of the heart.

What is the "cardiac excitation wave"?

Where does the contraction of the heart begin?

What is the effect of tying a ligature about the auriculoventricular groove?

What is the speed of the cardiac excitation wave?

What is the latent period of the frog's heart muscle?

What is the time value of the block of the heart's contraction?

Describe the atrioventricular bundle.

What is the cause of the block? Give evidence.

What is meant by the refractory period of the heart beat?

Define compensatory pause.

What are the sources of the nerve fibers to the heart? Describe their course.

Discuss the effect of stimulation of the vagus on the heart beat.

How does stimulation of the vagus affect a demarcation current from the auricle?

Discuss the end apparatus by means of which the vagi inhibit the heart.

What is the effect of stimulation of the augmentor fibers on the heart beat?

Give the lengths of the latent periods of inhibition and acceleration.

What evidence that afferent fibers run from the heart to the central nervous system?

Discuss the function and the effects of stimulation of the central cut end of the depressor nerve.

Are the vagi and depressor nerves continuously active?

How do weak and strong stimulation of sensory nerves affect the heart?

What effect has dilatation of the stomach on the heart?

Discuss the situation and action of the cardio-inhibitory centre.

Discuss the action of the accelerator centre.

What is the peculiarity in the distribution of bloodvessels to the heart?

What is an infarct?

How does the anemia resulting from hemorrhage differ in its action from that caused by ligating the coronary artery?

How do the contractions of the heart favor the entrance of blood into the coronary arteries?

In what ways does the blood supply to the heart affect its beat?

Discuss the constituents of the blood that cause the rhythmic activity of the heart.

How do the actions of potassium and calcium salts differ?

What is Ringer's solution?

What effect has carbon dioxide on the heart?

Why does the blood move from the arteries to the veins?

How is blood pressure measured?

Describe a mercury manometer.

What is the form of blood pressure curves obtained from an artery?

What is meant by mean blood pressure?

What are the mean blood pressures in arteries, capillaries, and veins?

What is the cause of the high pressures in the arteries?

What are the causes of blood pressure in capillaries and veins?

Why does the pressure decline from arteries to veins?

Why is there no pulse in the veins?

Discuss the action of subsidiary forces that aid the heart in circulation.

What is the pulse? Its cause?

How does the character of the pulse vary?

What is a sphygmogram?
What is the dicrotic wave? Its cause?
How are rapid changes in the velocity of the blood measured?
Give the rate of flow of the blood and the causes for its variations.
How long does the blood remain in the capillaries?
How does the pulmonary differ from the systemic circulation?
What governs the distribution of the blood in the body?
Discuss the distinction between vasoconstrictor and vasodilator nerves.
Describe the vasomotor centre.
What is the evidence for the existence of subsidiary centres controlling bloodvessels?
What are Traube-Hering waves?
What are pressor and depressor fibers?
Indicate a physiological compensatory blood-pressure mechanism.
Is there a chemical regulation of the caliber of bloodvessels?
Describe the lymph.
Describe fully the circulation of the lymph.

CHAPTER VII

RESPIRATION

THE expression respiration embraces two distinct ideas. It may mean the entrance of oxygen into and the exit of carbon dioxide from an animal, or it may have reference to the visceral —muscular and pulmonary, etc.—movements by which these gases are caused to flow in and out of the lungs. The lungs of man are of vital importance in the interchange of oxygen and carbon dioxide, while the skin is of but subsidiary importance. This condition of affairs is reversed in the frog. The lungs consist of an enormous number of *air vesicles* or *alveoli*, which communicate by means of a series of passages with the trachea and the external air. Their total area is more than one hundred times the superficial area of the skin, and their walls form a delicate partition in intimate relation to the blood capillaries of the lung. Before birth the lungs are airless (*atelectatic*), but after having once been expanded, they never regain their atelectatic condition, because during collapse the passages close first and so imprison some air in the alveoli. This fact forms the basis of an important medicolegal test. The lungs are enclosed in the air-tight thorax, and separated from its walls by a double layer of *pleura*. The thorax of the child grows faster than the lungs, so that the latter become distended in an air-tight cavity. Whenever the thorax is opened, the lungs, owing to the elasticity of their structure, immediately shrink together. It follows, therefore, that the lungs are always tending to shrink and thus pulling away from the thoracic walls and diaphragm. This produces a pressure in the pleural cavity below that of the atmosphere, and it is called a *negative pressure* whenever atmospheric pressure is regarded as a standard. The negative pressure has been found to vary greatly under different conditions, but may be put at minus 4.5 mm. Hg at the end of a quiet expiration, and

at minus 7.5 mm. Hg at the end of a quiet inspiration. During forced inspiration the value may reach minus 40 mm. Hg. The pressure in the pleural cavity — i. e., outside of the lungs and within the thorax—is known as *intrathoracic* pressure, while that within the lungs and respiratory passages is called the *intrapulmonary* pressure. The variations in pressure are caused by changes in the capacity of the thorax, which may enlarge in all directions. It is obvious that when the thorax increases in size the decreased pressure within allows the entrance of air from the outside, where it is at a higher pressure. The air rushes through the trachea and inflates the lungs. This constitutes an *inspiration*. The opposite process, or an expulsion of air by a decrease in the size of the thorax, is *expiration*, and both together form respiration. The lungs during respiration are entirely passive, and merely follow the thoracic walls because the atmospheric pressure acting on their inner surfaces is greater than that between the lungs and the thoracic walls. The pleuræ are moistened with lymph, and slide over each other without friction.

Inspiration is an active process brought about by certain muscles which, by their action, enlarge the thorax in a vertical, anteroposterior, and lateral direction. The upper part of the thoracic cage being fixed, the vertical diameter is increased by the descent of the diaphragm in contracting. Other muscles act on the ribs, with the result that their sternal ends are raised up and carried forward, enlarging the anteroposterior diameter; at the same time the direction of the axes of rotation of the ribs causes them to rotate outward and upward, so increasing the lateral diameter. The chief *muscles of inspiration* are the diaphragm, the scaleni, the serrati postici superiores et inferiores, the levatores costarum breves et longi, and the external intercostals and interchondrals. The diaphragm projects into the thoracic cavity in the form of a flattened dome. During contraction it descends from 5.5 to 11.5 mm. in quiet respiration, and about 42 mm. in deep inspiration. There is a tendency for the diaphragm to pull in its points of attachments—the lower ribs, with their cartilages, and the lower portion of the sternum, but usually this is counterbalanced by the pressure of the abdominal viscera. The serrati postici inferiores assist the diaphragm by fixing the

ninth, tenth, eleventh, and twelfth ribs. The scaleni fix the first and second ribs. The serrati postici superiores help to fix the second rib, and raise the third, fourth, and fifth ribs. The external intercostals and interchondrals and the levatores costarum elevate and evert the first to the tenth rib. They serve also to give the intercostal tissue a proper tension.

During *forced inspiration* additional muscles are brought into play to permit a more powerful inspiratory act. Besides the muscles already enumerated, the following are brought into play: The trapezei and rhomboidei fix the shoulders; the pectorales majores and minores, acting from the fixed shoulders, draw the sternum and ribs upward; the sterno-mastoidea fix the upper part of the chest; the erectores spinæ stiffen the vertebral column; the serrati postici inferiores, quadrati lumborum, and sacrolumbales draw the lower ribs downward and backward.

At the close of inspiration the various muscles that raised the thorax gradually relax, and by its weight the thorax compresses the lungs and expels the air. In addition there is an active recoil of the elastic tissue in the substance of the lung, which has been put on the stretch during inspiration. Also during inspiration the interosseous portions of the internal intercostal muscles were put on a stretch; when expiration begins these muscles contract, but their contraction is not sufficiently forcible to pull the ribs down, and the only purpose of this contraction seems to be to keep the intercostal tissues tense and thus prevent bulging of the intercostal spaces. During inspiration each costal cartilage is twisted in the direction of its long axis by the eversion of the ribs. During expiration the costal cartilage tends to untwist itself. It may be said there are *no muscles* of *quiet expiration*. *Forced expiration* is accomplished by the intervention of many muscles.

The interosseous internal intercostals act forcibly in drawing down the ribs when the lower part of the thorax is fixed; the abdominal muscles fix the lower part of the thorax and press the abdominal contents upward; the levatores ani and perineal muscles hold the floor of the pelvis rigid against abdominal pressure; the triangularis sterni draws the costal cartilages down.

A number of movements which take place in connection

with the ingress and egress of air to the lungs are known as *associated respiratory movements.* The nostrils may dilate with inspiration and return to their passive condition with expiration. The soft palate moves to and fro; the glottis is widened and narrowed. During labored breathing the mouth is opened and the muscles of the face become active; the soft palate is raised and the larynx is lowered.

It is stated that of the two types of respiration, "thoracic" and "abdominal," the former is more marked in women and the latter in men. This is true in the sense that women increase the anteroposterior and the lateral diameters of the chest more than do men, owing not so much to functional differences between the sexes as to habits of dress, etc. Adult males and children of both sexes use the diaphragm almost exclusively in quiet inspiration.

When the ear is placed in contact with the chest wall or a stethoscope is used, a *respiratory murmur* will be heard— fairly marked during inspiration; short and faint during expiration. It varies in different parts of the chest wall, being loudest over the large bronchi. The changes in these murmurs incident to disease of the respiratory tract are characteristic of different pathological changes, and it is upon the recognition of these alterations that the value of auscultation depends. The force of the inspiratory muscles is greatest in people of medium height, being equivalent on the average to a column of mercury three inches high. It diminishes in people above and below this height. The force of expiration is about one-third greater; but the variations are not so regular, since the expiratory muscles are used for other purposes, so becoming stronger. The value of breathing through the nose instead of the mouth consists in that it warms the air and moistens it; foreign particles are partially removed and noxious odors detected.

Normal respirations may be studied in man by means of the stethograph or the pneumograph of Marey. It is found that inspiration and expiration follow each other without pause; that inspiration is shorter, and that the curves of each differ in minor respects only. In pathological cases there may be expiratory or inspiratory pauses. The *Cheyne-Stokes* respiration consists of groups of ten to thirty respiratory movements, which are shallow at first, but become deeper

and deeper until a maximum is reached, after which they gradually become shallow again. The intervals between the groups last from thirty to forty-five seconds. The time ratio of inspiration to expiration may be put at 5 to 6. In infants the ratio is 1 to 2 or 3. The *rate* of respiration varies with the most diverse internal and external conditions. In the normal adult the rate is about 18 cycles a minute when the body is in repose. The ratio to the pulse rate may be put at 1 to 4. During quiet respiration the inflow and outflow of air, which amounts to about 500 c.c., is known as the *tidal air*. The volume of expired air, owing to its increased temperature, is greater than that inspired, but the actual quantity is less. *Complemental air* (about 1500 c.c.) is the amount that can be inspired after an ordinary inspiration. The *supplemental* or *reserve* air (about 1500 c.c.) is the amount that can be expelled after an ordinary expiration. *Residual air* is the volume that remains in the lungs after the most forcible expiration (1500 c.c.). *Vital capacity* is equal to the sum of the complemental, tidal, and supplemental air. *Stationary air* is the amount that remains after the ordinary expiration, and is equal to the sum of the reserve and the residual air. The *lung capacity* is the total quantity of air that can be held after the most forcible inspiration, and is equal to the sum of the vital capacity and residual air (4500 c.c.).

It may easily be calculated that man, in twenty-four hours, respires about 10,800 liters of air, which is equal to a space eight feet in three dimensions. The air, thus breathed, should be kept as nearly as possible of the composition of the atmosphere outside. The relative purity of room air may be most easily judged by a quantitative determination of carbon dioxide. Ordinary air contains 4 parts per 10,000. *Ventilation* should be sufficient to keep the carbon dioxide down to 6 parts per 10,000, giving a permissible degree of vitiation of 0.02 volume per cent. On this basis the air necessary for each person can be determined from the formula $d = \dfrac{e}{r}$, in which d represents in liters the delivery of fresh air per hour; e, the carbon dioxide expired per hour in liters; and r, the ratio of permissible vitiation. The value of d, then, is equal to 100,000 liters of air per hour for each person. The

ratio of the quantity of oxygen absorbed to the carbon dioxide given off is known as the respiratory quotient. While in the lungs the air loses 4.78 volumes of O_2 in 100, and gains 4.34 volumes of CO_2 in 100, so that the value of the *respiratory quotient* $\dfrac{4.34}{4.78}$ is equal to 0.901. This value is subject to great variations, because the production of carbon dioxide is to some extent independent of the amount of oxygen absorbed. This is so for several reasons:

1. CO_2 may result not only from oxidation changes, but from intramolecular splitting, so that the elimination of CO_2 in normal quantity may continue when absorption of O_2 has entirely ceased.

2. Some foodstuffs require more O_2 for their complete oxidation than others.

The air during its sojourn in the lungs is altered in addition to its O_2 and CO_2 contents by assuming the temperature of the body, regardless of the temperature of the outside atmosphere; by an increase of its aqueous vapor; and possibly, by the presence of volatile organic bodies. The nitrogen remains unchanged. The quantity of water lost by the lungs varies inversely with the amount in the atmosphere, and directly with the quantity of air inspired. The blood in its passage through the lungs becomes aërated. The O_2 and CO_2 in arterial and venous blood together form about 60 volumes of the blood in 100. The proportions of the gases to each other are constant in the arterial blood, but vary in the venous blood in different localities.

The oxygen of the air enters the alveoli of the lung, passes into the blood through the delicate epithelial walls, and is carried to the tissues, where it is taken up by the cells. Very little is used up in the blood. The CO_2 given off by the cells is carried to the alveoli of the lungs by the blood, and is there given off. It becomes necessary, therefore, to consider the methods by means of which the *interchange of gases* is brought about. The air currents that are set up mechanically probably help to equalize the composition of the air in the lungs. Besides, the heart with each contraction as it shrinks in size expands the lungs slightly and causes a movement of air into the chest synchronous with its beat. These are known as *cardiopneumatic*

movements. In addition to the mechanical factors, the physical process of diffusion is of great importance. The rapidity of diffusion depends, among other things, upon the differences of the partial pressures of the gases in various regions. If the total atmospheric pressure is 760 mm. Hg, and O_2 forms $\frac{1}{5}$ of the gaseous constituents of the air, then it will exert a pressure of its own equal to $\frac{1}{5}$ of 760, or 152 mm. Hg; and carbon dioxide, forming 0.04 volume in 100 of the air, will exert a pressure of $\frac{0.04}{100}$ of 760, or about 0.30 mm. Hg. It has been estimated that the partial pressures of O_2 and CO_2 in alveolar air are equal to 100 and 35 mm. Hg respectively. The differences in partial pressures, therefore, will cause O_2 to diffuse toward the alveoli, and CO_2 from the alveoli to the outside air.

The gases in the blood are not only in solution, but also in weak chemical combination, so that diffusion from the alveoli into the blood and *vice versa* is somewhat complicated. The amount of a gas that is absorbed when brought in contact with water depends upon the relative solubility, the temperature, and the barometric pressure. Each, of a mixture of gases, is absorbed independently of the others. The relative solubility is expressed by the *coefficient of absorption* of the fluid, which is experimentally determined, and is found to be in inverse ratio to the temperature and in direct relation to the pressure. The absorption coefficient of water for O_2, as an example, at zero Centigrade and 760 mm. pressure, is equal to 0.0489. This means that under the given conditions of temperature and pressure 1 volume of water will take up 0.0489 volume of O_2. Since, however, the O_2 forms but $\frac{1}{5}$ of the quantity of the air, water will absorb from the atmosphere only $\frac{1}{5}$ of 0.0489 volume, which is equal to 0.009+, or nearly 0.01 volume. As the partial pressure of O_2 is raised or lowered, O_2 will leave or enter the water, so that the gas in solution is said to be under *tension*. The absorption coefficient of blood for O_2 is about that of water, but at the bodily temperature is decreased to less than $\frac{1}{2}$. Every volume of blood should, therefore, contain $\frac{1}{2}$ volume of oxygen in 100; but experiment shows that there is much more present. Upon subjecting blood to a vacuum, O_2 is given off according to the laws of partial

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pressures and tensions until the pressure is lowered to $\frac{1}{10}$ of an atmosphere. From $\frac{1}{10}$ to $\frac{1}{30}$ of an atmosphere the great bulk of O_2 is given off. Below $\frac{1}{30}$, physical laws, as given above, again prevail. The explanation of this is that the O_2 is held in chemical combination with the hemoglobin, and is set free at $\frac{1}{10}$ to $\frac{1}{30}$ of an atmosphere. This pressure is termed the *tension of dissociation*.

Venous blood contains 45 volumes of CO_2 in 100. Of this, 5 per cent. is in simple solution, 10 to 20 per cent. in firm chemical combination, and 75 to 80 per cent. in loose chemical combination. The largest amount is connected with the red blood cells. While the CO_2 absorbed by water increases regularly with the increase of pressure, that absorbed by solutions of hemoglobin is relatively large for low pressures and small for high pressures. The quantity in the blood is in excess of what physical laws will permit. It is found that the partial pressures of O_2 and CO_2 in venous blood are about 22 and 41 mm. Hg respectively. Comparing the pressures of O_2 in the lung, alveoli, blood, and tissues (152, 100, 22, 0) with those of CO_2 (0.3, 35, 41, 58), it is seen that O_2 and CO_2 will diffuse in opposite directions. Pure oxygen at a pressure of 1 atmosphere may be breathed without injury. At higher pressures it acts as an irritant and produces inflammation. When less than 10 volumes of oxygen are present in the air in 100, it is insufficient to maintain the life of man. Pure CO_2 is fatal in from two to three minutes. N, H, and CH_4 cause no inconvenience if sufficient O_2 is present. Nitrous oxide and ozone produce anesthesia, and finally death. Air containing 20 volumes of CO_2 in 100 is rapidly fatal.

Eupnea is normal, easy breathing. *Apnea* is a condition of suspended breathing. *Hyperpnea* is increased respiratory activity. *Polypnea* is a condition of deep, labored breathing. *Asphyxia* is characterized by convulsive breathing, followed finally by infrequent and feeble respirations. Apnea can be induced in man or animals by rapid, deep respiratory movements or by forcing air into the lungs with a bellows. It is brought about by using pure O_2 or H_2; lasting for a longer time when the former is used. But the fact that it can be produced with H_2 shows that the condition cannot be due to a superabundance of O_2 in the blood. It is believed that in

the violent inflation of the lungs the sensory endings of the pneumogastric in the lungs are stimulated, which produces a temporary inhibition of the respiratory centre. The diminution of the CO_2, however, is the principal cause for this condition. The presence of CO_2, more than the absence of O_2, is the normal stimulus of the respiratory centre.

Hyperpnea may be produced by the products of muscular activity. The nature of these products is unknown, but the decreased alkalinity of the blood indicates that they may be of an acid character. Polypnea is due to direct stimulation of the respiratory centre, through the temperature of the blood or through reflex excitation of cutaneous nerves. Dyspnea may be the result of a deficiency of O_2, or due to an excess of CO_2, in the blood. Oxygen dyspnea is characterized by frequent deep inspirations; carbon dioxide dyspnea, by infrequent, vigorous expirations. In the former, death is severe; there is a marked rise of blood pressure and violent convulsions. In the latter, death takes place more quietly, the blood pressure rises less, and no motor disturbances are present.

Asphyxia is divided into three stages: (1) One of hyperpnea; (2) one of dyspnea and convulsions; (3) one of collapse.

If asphyxia is brought about by ligating the trachea, the process lasts for four or five minutes. The first stage lasts one minute, the second a little longer, and the third from two to three minutes. If produced by a very gradual deprival of air, there may be no motor disturbances. In the first stage the respirations are increased in depth and frequency. Inspiration is pronounced. During the second stage expirations become violent and convulsive. During the third stage respirations are shallow, the pupils dilated, motor reflexes disappear, consciousness is lost, convulsive twitches are present, the limbs are stretched and rigid, the head and body arched backward, and finally the heart ceases beating. During the first and second stages the gums, lips, and skin become blue, the heart beats are less frequent, and the blood pressure is increased. During the third stage a general depression ensues. After death the blood is almost black, the arteries empty, and the veins and lungs congested. Death from drowning is due usually to asphyxia, but sometimes is due to a cessation of the activity of the heart.

The respiratory movements have a marked effect upon the blood pressure. In the carotid artery with every inspiration it rises, and with every expiration it falls (Fig. 7). The two events are, however, not exactly synchronous, the pressure changes lagging a little behind the respiratory changes. The effects are readily understood when it is remembered that the thoracic cavity is an air-tight chamber, and that the elastic fibers of

Fig. 7
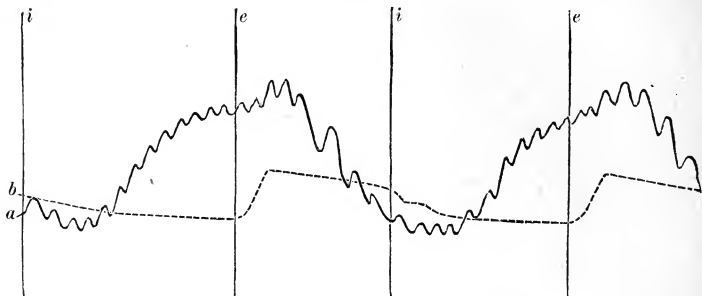
Comparison of blood-pressure curve with curve of intrathoracic pressure (Foster) (dog): *a* is the blood-pressure curve taken by means of a mercury manometer; it shows the respiratory undulation, the slower beats on the descent being very marked; *b* is the curve of intrathoracic pressure obtained by connecting one limb of a manometer with the pleural cavity. Inspiration begins at *i*, expiration at *e*. With the beginning of inspiration (*i*) the expansion of the chest causes a marked fall of the mercury in the intrathoracic manometer; but the effect soon diminishes, since the lessening of intrathoracic pressure does not bear on the manometer alone, but on the lungs also; and as the lungs expand more and more the fall in the mercury becomes less and less until toward the end of inspiration the curve becomes very nearly a straight line. Conversely, the return of the chest at the beginning of expiration (*e*) produces at first a marked rise of the mercury in the manometer; but this soon ceases as the air leaves the chest and the lungs shrink, whereupon the mercury falls slowly.

the lung which fill it are constantly pulling on the heart and bloodvessels. This effect is increased during inspiration when the thorax is enlarged. The pressure of the blood is consequently lowered in the intrathoracic vessels, and the blood rushes in from extrathoracic regions, where it exists under atmospheric pressure. The effect of the pull of the lungs is greater upon the flaccid walls of the veins than upon the more rigid walls of the arteries, so that the inflow through the veins

is favored more than the outflow through the arteries is hindered. The pulmonary circulation is favored also by the increased negative pressure during inspiration, since the lung fibers pull with greater effect on the pulmonary veins than on the pulmonary artery, which produces a greater difference in pressure in the two vessels, so accelerating the flow of blood. During expiration there is not only a return to the former condition, but the intrapulmonary capillaries are actively squeezed between the air in the lungs and the thoracic walls. This again aids the flow in its passage from the right to the left side of the heart. The pressure which inspiration through the descent of the diaphragm exerts on the abdominal organs will force the blood along the arteries toward the limbs and check somewhat its exit from the thorax. In like manner the pressure on the veins will force the blood into the thorax and momentarily check its flow from the lower extremities. Finally, the heart rate is increased distinctly during inspiration. The combined action of the above factors is to draw an increased amount of blood into the thorax and to the left ventricle, which, having more blood to pump, raises the blood pressure. It requires some time for the increased amount of blood to reach the left ventricle, and, as a result, the true effect of inspiration on the blood pressure in the aorta is not felt at the very beginning of the act, but comes a little tardily. This delay may be so great in some animals as to produce, apparently, an inversion of the time relations.

Respiratory Centre.—Respiration may continue after destruction of the entire brain except the bulb, where the centre controlling respiration is situated. The area described by Flourens as the *nœud vital* is located at the level of the calamus scriptorius. The centre is bilateral, one-half being situated on each side of the median line and corresponding in location to the position of the tractus solitarius. The two parts are intimately connected by commissural fibers, but may be separated by a section in the median line, after which respiration may continue in a normal manner. But each half is connected with the lung and muscles of respiration of the corresponding side, so that if destroyed the movements on its own side cease.

The respiratory centre is automatic in its activity, but it is influenced by the sensory fibers of perhaps all of the cranial

and spinal nerves and also by intracentral paths, passing from the cerebrum to the medulla. The effect of sensory impulses on the respiratory centre is varied. In general, however, stimulation of cutaneous nerves gives one of two effects; either a stimulating action, shown by more active inspirations and expirations, or an inhibitory effect in which respirations become slower and feebler and may cease altogether. It is customary, therefore, to speak of *respiratory pressor* and *depressor fibers*. The rhythm of respiration may be affected by the will and by the emotions, by the quality, and the temperature of the blood, and by afferent impulses, coming particularly over the tenth nerve. Section of the latter on one side may slow and deepen respiration while section of both vagi almost invariably exaggerates this effect leading to distinct pauses between the respiratory movements. When the central end of the cut vagus is stimulated, respiration is affected in a variety of ways depending upon the strength of the stimulus and the condition of the centre. With weak stimuli the inspiratory movements are inhibited partially or completely, leading to a cessation of respiration with the thorax in the stage of passive expiration. Or, the rate of the inspiratory movements may be increased and thus lead to cessation of respiration with the thorax in an inspiratory position. These effects are interpreted as due to two sets of fibers: (1) *Inspiratory* fibers whose effect is to quicken the rate of discharge of the respiratory centre, and (2) *inspiratory inhibiting* fibers whose effect is to inhibit, partially or completely, the discharges of the respiratory centre. Excitation of the superior laryngeal fibers always inhibits respiration— the chest coming to rest in the position of passive expiration. Excitation of the glossopharyngeal nerves has a similar effect, but the inhibitory influence lasts for three or four successive respiratory acts. Irritating gases affect the trigeminal nerve endings in the nose or the endings of the tenth nerve in the larynx and lungs. The effect of the excitation of the cutaneous nerves may be seen in a cold douche, which primarily increases the respiratory rate and may cause its cessation.

The efferent respiratory nerves are the phrenics, which supply the diaphragm, certain spinal and cranial nerves supplying respiratory muscles. Section of one phrenic causes paralysis

of the diaphragm on the corresponding side. Section of the cord just below the fifth cervical nerve stops the costal movements, but does not affect the diaphragm, because the nuclei of origin of the phrenics lie just above the section. If the section is placed somewhat higher, respiration ceases entirely, but the associated movements of the larynx and face continue. During forced breathing the facial, hypoglossal, and spinal accessory nerves are called into action. During uterine life the respiratory centre is in an apneic condition, on account of a low irritability of the respiratory centre.

Cases have been seen in which the child has made respiratory efforts while within the intact fetal membranes. Such an attempt draws some of the amniotic fluid into the nose, causing inhibition of all further efforts. *After birth, when spontaneous respiration is about to take place, it is well to remove all mucus or other matter from the nose, to avoid inspiration of them.*

Normal, quiet respiration may be regarded as consisting of an active inspiration and a passive expiration. It is the coördinated activity of the inspiratory muscles that is characteristic of respiration, and the expiratory muscles come into action only occasionally under special conditions. Periodically the respiratory centre becomes active as the result of the stimulating action of the carbon dioxide of the blood. The inspiratory act follows and continues until the inhibitory fibers in the vagus, stimulated by the expansion of the lungs, brings inspiration to an end. The expiration which follows is, in quiet respiration, a passive return of the chest to its original condition. In other words, the expiratory centre is not, under ordinary conditions, automatic. Its activity is, in some way, dependent upon that of the inspiratory centre. Under special conditions it becomes active: (1) In reflexes like coughing; (2) voluntarily, as in straining; (3) as the result of the stimulation of pain fibers; (4) by the action of substances, CO_2 and others, in the blood.

The bronchial musculature is supplied through the vagus with motor and inhibitory fibers, or, as they are called, bronchoconstrictor and bronchodilator fibers. An artificial tonus of the constrictor fibers can be produced by the administration of a number of drugs such as muscarin, pilocarpin, and physostigmine. They are supposed to stimulate the endings of the

autonomic fibers in the lungs, and their effect may be removed by atropine. Bronchoconstriction can be excited by stimulating the nasal mucous membrane, particularly a small area well back on the nasal septum. Cauterization of a corresponding area in man is said to give permanent relief in cases of spasmodic asthma which is associated with spasm of the bronchial muscles. These fibers are also stimulated during the excitatory stages of asphyxia.

There are a number of involuntary and voluntary special respiratory acts, largely reflex, which result from modifications of inspiration and expiration.

Sighing.—This results from a prolonged inspiration, the air passing noiselessly through the larynx and being expelled rather suddenly.

Hiccough.—The inspiration is sudden, and terminated by closure of the glottis.

Cough.—This results from a deep inspiration followed by a forced and sudden expiration, during which the glottis is closed momentarily by the spasmodic action of the vocal cords.

Sneezing.—In this case after a deep inspiration the air is directed through the nasal passages by a sudden and forced expiration.

Speaking.—In this case there is a voluntary expiration, and the vocal cords being rendered tense by their muscles vibrate as the air passes over them, producing sound.

Singing.—This varies from speaking only in the differing tension and position of the vocal cords and the consequently different sounds produced.

Sniffing.—This results from rapid repeated but incomplete nasal inspirations.

Sobbing.—This consists of a series of convulsive inspirations, during which the glottis is more or less closed.

Laughing.—This results from a series of short and rapid expirations.

Yawning.—This is an act of inspiration more or less involuntary, accompanied by a stretching of various facial muscles.

Sucking.—This is caused chiefly by the depressor muscles of the os hyoides, which, by drawing down and back the floor of the mouth, produces a partial vacuum in it.

QUESTIONS OF CHAPTER VII

What two different meanings are included in the term respiration?
What purpose do the lungs of man serve?
What is the total area of the alveoli of the lung?
What is the condition of the lungs before birth?
What are inspiration and expiration?
Why do the lungs follow the walls of the thorax?
In what directions is the thorax enlarged in inspiration?
Why does the air enter the lungs in inspiration?
Tell in detail by what mechanism the thorax is enlarged in inspiration.
What are the chief muscles of inspiration?
Give the action of each.
How is expiration brought about?
Give the action of the muscles of forced expiration.
What are associated respiratory movements?
Describe the character and significance of respiratory sounds.
What is the force of the respiratory muscles equal to?
What is the value of nasal breathing?
Describe a respiratory tracing.
Describe the Cheyne-Stokes respiration.
What are the relative lengths of inspiration and expiration?
What is the rate of breathing, and how is it varied?
Define and give values of tidal air; complemental and supplemental air; residual air and vital capacity.
What is the stationary air equal to?
What is the lung capacity?
What volume of air passes through the lungs of man in a day?
What is the respiratory quotient? Explain why it varies.
How is the air altered in the lungs?
How does the quantity of water vapor given off by the lungs vary?
How is the carbon dioxide held in the blood?
What is the evidence that CO_2 is held in chemical combination?
Compare the partial pressures of O_2 and CO_2 in the external air, alveoli, blood, and tissues.
What is the effect of breathing pure oxygen?
Give the effects of breathing other gases.
Define the terms eupnea, apnea, hyperpnea, polypnea, dyspnea, and asphyxia.
Discuss apnea and its causes.
How is hyperpnea produced?
What is dyspnea due to?
Discuss asphyxia in detail.
What is death by drowning due to?
Give the time relations of the respiratory movements to the respiratory blood-pressure changes.
Explain in detail how respiratory movements produce changes in blood pressure.
What are the changes in the heart rate during respiration?
Discuss the respiratory centre in the medulla.
What can be said of other respiratory centres?
What is the proof that the bulbar respiratory centre is automatically rhythmic?
Discuss the expiratory centre.
Discuss the innervation of the bronchial muscles.
What happens to the blood in its passage through the lungs?

What is the amount of O_2 and CO_2 in the blood?

What factors bring the O_2 of the air to the alveoli of the lung?

What are cardiopneumatic movements?

Explain what is meant by the partial pressure of a gas.

Explain in detail the diffusion of O_2 from the outer air into the alveoli.

In what ways are the gases of the blood held?

What factors govern the amount of a gas absorbed by a liquid?

What is meant by the coefficient of absorption?

In what way is the gas in the blood under tension?

How much oxygen should the blood take up according to physical laws? Does it in reality hold more or less?

How is the discrepancy explained?

What is meant by tension of dissociation?

How may the respiratory rhythm be affected?

What is the effect upon the respiration of sectioning the vagi? Of stimulation of the central end?

What are the afferent nerves that control the activity of the respiratory centre?

What is the effect of excitation of the superior laryngeal and glossopharyngeal nerves?

Through what nerves do irritating gases affect respiration?

What afferent nerves are involved in respiration?

What is the effect of sectioning a phrenic nerve?

Give the effect of sectioning the cord just below the fifth spinal nerve.

Discuss the condition of the respiratory centre in the fetus.

What nerves are distributed to the lung tissue?

Discuss the kinds of fibers in the vagus which are supplied to the bronchi.

What does stimulation of the central and peripheral ends of the fibers bring about?

Define sighing, hiccough, cough, sneezing, speaking, singing, sniffing, sobbing, laughing, yawning, and sucking.

CHAPTER VIII

METABOLISM

HAVING traced the food to its reception in the blood, it will be proper to consider the facts that are known concerning its further history. The absorbed materials are rapidly carried to all portions of the body, and in the capillaries are transferred through their walls to the lymph or tissue fluid, which, in turn, brings them into intimate contact with the tissue cells. Each cell extracts from the fluid which bathes it the substances that it needs for its nourishment. Then, under the influence of living matter or its products (enzymes), these substances undergo a series of changes, anabolic and katabolic in nature, which converts them finally to simple stable bodies possessing little energy.

Energy of Food.—The law of the *conservation of energy* teaches that the sum total of energy of the universe is constant, and that it can be neither created nor destroyed, or, in other terms, increased or diminished. This law is as rigorously true for the body as for any physical system, so that the manifestations of living bodies must be the transformations of energy brought to them in some form or other. Of all the sources of energy to the body, the chemical energy of the food is the most important. It is in a potential form, and reappears in the body in kinetic form as *heat, electricity,* and *mechanical work*. By far the greatest amount appears as heat. An adult man in the course of twenty-four hours will liberate about 2,400,000 calories of heat—a *calorie* being equal to the amount of heat which is required to raise one cubic centimeter of water one degree Centigrade.

Since the energy of foodstuffs is set free by their physiological oxidation, it is obvious from the standpoint of the doctrine of the conservation of energy that it may be measured by burning the foodstuffs outside of the body. This is done

by means of a *calorimeter*, and the number of calories of heat obtained is known as the *combustion equivalent*. This, in round numbers, for proteins, has been found to be 4100 calories; for fats, 9300 calories; and for carbohydrates, 4100 calories. These foodstuffs, so far as their potential energy is concerned, are interchangeable, so that if carbohydrates are to take the place of fats, they must be furnished in the ration of 9300 to 4100 or as 2.2 to 1. In other words, it takes more than twice as much carbohydrate material to render the same energy as any given amount of fat. This ration of 1 to 2.2 is known as the *isodynamic equivalent*.

The energy produced by the body in twenty-four hours may be measured as heat in two ways:

1. It may be measured directly by placing the animal in a calorimeter.

2. It may be obtained by feeding on a given diet, determining from the excreta the amount of food destroyed, and multiplying by the proper combustion equivalent. These methods are known respectively as *direct* and *indirect calorimetry*. The nutritional value of foodstuffs cannot be estimated from their contained energy alone, and it is necessary to follow the changes they undergo in their metabolism as far as it is possible.

Metabolism of Proteins.—The decomposition of the protein molecule during digestion may be said to have a number of purposes: (1) It facilitates the absorption of this foodstuff; (2) it is, very probably, desirable that such digestion products as proteoses and peptones do not appear in the blood, for if injected into the circulation they cause profound disturbances and are rapidly excreted by the kidneys; (3) food proteins cannot be used directly in the formation and repair of protoplasm, since the tissue proteins differ from the food proteins, as well as from each other, in the amount and kinds of amino-acids entering into the structure of their molecules; (4) under ordinary conditions meals contain a surplus of nitrogen which must be gotten rid of because unnecessary to the needs of the tissues. This is done by the conversion of superfluous amino-acids and poisonous ammonia compounds into innocuous urea.

It follows, therefore, that there are distinguishable two paths of protein metabolism. The metabolism that takes

place along one path varies extremely, in a quantitative sense, with the amount of protein in the food. The chief end products formed are urea and inorganic sulphates. This form of katabolism is not essentially connected with the life and nutrition of living substance of the body as a whole, and is, therefore, termed *exogenous*. The other form of protein metabolism is practically constant in amount for any given individual, and is independent of the quantity of protein in the food. The characteristic end products formed are kreatinin and neutral sulphur. Since it is an expression of the metabolism of the living material of the body itself, it is termed *endogenous* metabolism.

The blood proteins, serum albumin and serum globulin, particularly the former, have been looked upon as a resynthesis of part of the digestion products, and this function has been attributed to the intestinal mucosa. If this is the case, then the proteins must again be decomposed in the cells of the various tissues in order that the amino-acids may be recombined into tissue proteins. On the other hand, it is conceivable, that only a moderate synthesis takes place in the intestinal wall, sufficient for tissue needs, and that the blood proteins are material proper to the circulating tissue, blood. They might thus serve as a storehouse of protein material to be drawn upon in case of starvation. In the latter condition it is said that serum albumin is relatively decreased while serum globulin is increased. They may, therefore, have a double source—the former being more closely related to food proteins; the latter, to tissue proteins. Eventually, it is believed, they as well as other more complex body proteins disintegrate into comparatively simple nitrogen-containing substances which appear in the urine as urea, uric acid, kreatinin, and other bodies.

Formation of Urea.—Urea is found in the blood of man to the extent of 0.04 to 0.06 per cent. Since urea is a waste substance and the kidney an excretory organ, it is a simple matter to conclude that the urea of the urine is separated from the blood by the kidney. All evidence tends to show that the kidney itself is a very unimportant seat of urea manufacture. Muscle, likewise, though forming three-fourths of the proteins of the body, contains only a trace of urea. The liver, on the

other hand, contains a relatively large amount, and the evidence is very strong that it is the organ in which urea is mainly but not exclusively found.

1. When an excised liver is perfused with ammonium carbonate or other salts of ammonium, these substances may be converted into urea, which is not the case when they are passed through muscle or kidney.

2. The blood during periods of digestion contains substances which, when perfused through a liver, may be changed to urea. This is not the case when the blood is taken from a fasting animal. Furthermore, the blood of the portal vein during digestion contains several times as much ammonia as does arterial blood. The excess disappears in the liver. It suggests that the intestine furnishes materials which the liver converts into urea.

3. The establishment of an Eck fistula in dogs, whereby the portal blood is transferred directly into the inferior vena cava, leads to a marked diminution of the quantity of urea excreted, but to an increase of the ammonium salts in the urine. If, at the same time, much protein is fed, characteristic convulsions are produced such as appear when ammonium salts are directly injected into the circulation.

4. In acute yellow atrophy or fatty degeneration of the liver the amino-acids and the ammonia formed in the intestines during digestion pass unchanged through the liver and are excreted by the kidney. Urea almost disappears from the urine, and leucin, tyrosin, etc., and ammonia compounds appear or are increased in quantity.

That the liver is not the only source of urea is shown by the fact that urea continues to be formed when the liver is removed. Some urea is formed in the tissues generally. The essential process in the manufacture of urea is still a matter of investigation. In the laboratory it may be formed from protein either by hydrolysis or oxidation. Of the hydrolytic products of protein, one is arginin ($C_6H_{14}N_4O_2$), which by further cleavage forms urea and ornithin. A special ferment, arginase, found in the liver produces this cleavage. Other ferments, de-amidizing ferments, break up ornithin by removing the amide groups leading to its conversion to ammonia and urea. It is important to bear in mind that the hydrolytic cleavage

associated with the breaking up of protein into amino-acids reduces their available energy but little. This too, most likely, is true of the separation of the nitrogen from amino-acids, leaving thus a residue rich in carbon, with almost the same potential energy as the original protein. Finally, it may be said that under the influence of a special uricolytic enzyme a part of the uric acid (one-half in man) may be converted to urea.

Formation of Uric Acid.—This waste product, like urea, is separated from the blood by the kidney. It is remarkably increased in gouty persons. There can be no doubt that in birds uric acid is the result, mainly, of a synthetic process in the liver. A similar but less pronounced process takes place in the liver of mammals, but the main source of uric acid lies in the breaking up and oxidation of nucleins, taking place in all the tissues of the body. A second source lies in the taking of food rich in nucleoprotein, or rich in purin bases, like Liebig's meat extract. When nucleoprotein is digested with gastric juice some protein is easily split off and yields the ordinary products of proteolysis. The insoluble residue is nuclein. The latter may be easily hydrolyzed by heating with dilute hydrochloric acid which yields another protein and nucleic acid. In order to break up nucleic acids it is necessary to heat in a sealed tube with hydrochloric acid. As a result, phosphoric acid, purin bases, and often, but not always, pyrimidin bases appear. Knowing the above, it is not difficult to formulate the manner in which uric acid results from the breaking up of nucleoproteins.

There are organs which contain ferments which split nucleoproteins. The resulting nucleins, together with those derived from the digestive tract, are decomposed by another ferment, nuclease, yielding phosphoric acid, a carbohydrate group, pyrimidin and purin bases. Among the latter are adenin and guanin. The ferments, adenase and guanase, remove the amino group from these purin bases, transforming adenin into hypoxanthin and guanin into xanthin. Now, by means of the ferment oxydase, hypoxanthin is oxidized to xanthin and xanthin to uric acid. The uric acid which comes from the food is distinguished as exogenous, from the endogenous portion derived from the tissues. The latter amounts to 0.6 gram

in twenty-four hours. Under constant conditions it is constant in the same individual. As has already been mentioned under urea, a uricolytic ferment is responsible for a considerable destruction of uric acid, which then leaves the body as urea. An absence of this ferment is supposed to be one of the factors in the production of gout.

The Formation of Hippuric Acid.—This constituent of the urine is of interest because it is formed by the kidney. If this organ be perfused with blood to which benzoic acid and glycin have been added, hippuric acid is produced. A ferment is supposed to be concerned in this reaction. Normally, most of the benzoic acid is derived from an aromatic nucleus in vegetable food, but in some animals the body tissues also serve as a source. Glycin is known to be a product of the metabolism of proteins and is also a constituent of glycocholic acid of the bile.

The Formation of Kreatinin.—Some kreatinin is, no doubt, derived from the kreatin of food ingested. Of the remainder excreted there is reason to believe that it represents the nitrogen given off in the wear and tear of the bodily machinery. During muscular work the elimination of kreatinin is increased. The amount excreted by different persons is related to the weight of the active tissue in the body. There are ferments in the body which have the power of changing kreatin to kreatinin and other ferments which destroy both.

Metabolism of Carbohydrates.—The main facts in the history of carbohydrate foodstuffs may be briefly stated. The digestive processes have converted them mainly, if not entirely, into dextrose. During digestion, particularly after a carbohydrate meal, the portal blood holds more dextrose than is present in blood generally. In fact, portal blood contains more dextrose than the hepatic vein, indicating that some of the sugar (12 to 20 per cent.) disappears during the passage of the blood through the liver. It is stored in the liver as glycogen; as such it may be visible microscopically, and from which it may be extracted with boiling water. If after the death of the animal the liver be left in place for some time, no glycogen can be extracted, but sugar is present in abundance. During the intervals of digestion sugar in the hepatic vein is twice as abundant as the sugar in blood generally or in that of the

portal vein. The glycogen, therefore, reconverted to sugar, is given back to the blood. This reconversion is effected by a diastatic endoenzyme called glycogenase. That it is an enzyme action and not due to the living cells is shown by the fact that glycogenase will do its work when minced liver is mixed with chloroform water.

During starvation, glycogen disappears from the liver cells. After such a period, a carbohydrate diet rapidly replaces the glycogen, a protein diet to a lesser extent, and a fatty diet little, if at all. Very decisive evidence that glycogen may be produced from proteins has been shown by feeding dogs with casein after the production of permanent glycosuria by removal of the pancreas. The amount of sugar excreted was much greater than could have come from the glycogen originally present in the animal's body plus free carbohydrate in the food plus prosthetic groups. That the sugar did not come from fat was shown by the fact that when the protein was increased the dextrose and nitrogen excreted increased proportionally. Glycogen may be formed on a fat diet, since it has been shown that glycerin is a glycogen former. This was shown directly by perfusing a tortoise liver with blood to which glycerin had been added. There is no proof that fatty acids can be converted to glycogen. The liver contains, normally, from 2 to 10 per cent. of glycogen, forming the main storehouse of surplus carbohydrate. Muscles contain from 0.3 to 0.5 per cent. per weight, and hold usually more than one-half of the total glycogen of the body. Glycogen tends to disappear from the organism under two general conditions — during muscular activity and during starvation, although the heart will retain its normal supply until the very last. Glycogen disappears much more readily than stored fat. It forms the most ready source of energy. It is very probable that most of the glycogen leaves the liver as sugar, but possible also that it may in the liver cells undergo a conversion to fat and leave in this form.

History of Dextrose.—The sugar in the blood varies from 1.5 to 3 parts per 1000. If the amount rises above this limit it is excreted by the kidneys. This occurs when large quantities are eaten. It is an important practical rule *that a person who can tolerate two grams of dextrose per kilo of body weight taken not less than two hours after a meal without excreting any of it*

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is free from incipient diabetes. Although a small amount of the sugar of the blood may undergo conversion to fat, the greater part is destroyed in all the active tissues of the body, particularly in the muscles and glands. The presence of a glycolytic ferment in the blood is rather doubtful. The most suggestive facts are those obtained by Cohnheim, who showed that the pancreas and muscle have, individually, no or very slight glycolytic power, but when combined have a very great glycolytic power. This is attributed to the activation of a ferment in muscle by a substance derived from the pancreas. The essential value of the pancreas is shown by the production of a permanent glycosuria which follows its extirpation.

Metabolism of Fats.—The greater part, if not all, of the fat undergoing digestion in the alimentary tract is converted into fatty acids and glycerin, and thus is absorbed by the intestinal mucosa. Some of this reappears as neutral fat in the thoracic duct, along which it passes into the blood stream. But it is very soon removed from the circulation. It is very natural to suppose that it is taken up by connective-tissue cells and stored, thus forming adipose tissue; and this, as a matter of fact, is true for a fraction of the fat. This is corroborated by experiments upon dogs in which foreign, easily detected fats, like linseed oil, mutton fat, etc., were fed. But, in addition, body fat is derived from other sources. It is derived from both carbohydrates and proteins. The proof that carbohydrates are directly responsible for some of the fat laid down is complete, and, in addition, they act as protein sparers so that the carbonaceous residue of the broken-down protein is shielded from oxidation and laid down as fat. This is inferred from experiments in which the addition of protein to a carbohydrate or fat diet, in larger amounts than is just necessary for nitrogenous equilibrium, led to a rapid increase in fat laid on. Although so very probable, absolute proof, qualitatively or quantitatively, of the direct conversion of protein to fat is not obtainable. Sooner or later fat is hydrolyzed and oxidized to carbon dioxide and water, furnishing in this transformation the energy which appears as heat, chemical and mechanical work. Many of the tissues of the body contain intracellular, soluble, fat-splitting enzymes, the lipases, intimately concerned with fat transformations.

Autolysis.—As a matter of fact, a great variety of enzymes, not only lipases, but oxydases, reductases, etc., are demonstrable in living tissues. No less than eleven ferments are said to be active in the liver alone, namely, a proteolytic and a nuclein-splitting ferment, a de-amidizing ferment, a fibrin ferment, a milk-curdling ferment, a bactericidal ferment, an oxidase, a lipase, a maltase, glycogenase, and an autolytic ferment. When a piece of liver is removed with aseptic precautions and kept at body temperature, an extensive autodigestion occurs in which ammonia and other basic substances, glycin, tryptophan, and tyrosin occur. Similar autolytic changes occur in other tissues, in pathological growths like carcinoma, and in the removal of such exudations as occur in pneumonia. The ferments in certain cases have been obtained in active condition in extracts.

Urine.—All the materials that enter the body and which take a part in the complex interplay of chemical changes that constitute living processes, sooner or later again leave the body as waste products, *i. e.*, they are excreted. By far the greater part of these appear in the urine, in the expired air, and in the feces. The carbon of the foodstuffs reappears chiefly in the carbon dioxide of the expired air; the hydrogen, as water in the urine, expired air, and perspiration, etc.; the nitrogen as the nitrogenous bodies of the urine.

The urine is the product of the secretory activity of the kidney cells. It is a clear yellow liquid, acid to ordinary indicators, but almost neutral by physicochemical tests. The average specific gravity is 1020, with normal extremes from 1005 to 1035. The average quantity per day may be put at 1200 c.c. to 1600 c.c., but it varies inversely with the activity of the sweat glands. The composition of the urine is very dependent upon the quantity and quality of food. The most prominent constituents besides water and inorganic salts are urea, uric acid, and allied purin bases, ammonia, hippuric acid, kreatinin, etc. Also organic bodies—indoxyl, phenyl, skatoxyl, etc., conjugated with sulphuric acid. These conjugated organic bodies are derived primarily from the digestive tract.

Determination of Metabolism.—It is a well-known fact that in an adult the weight of the body may remain constant for many years, even when the diet varies greatly in nature

and amount. It is inferred, and correctly, that the relative proportions of the different tissues of the body remain constant too. Under such conditions the expenditure of the body must exactly equal its income; otherwise, the balance would not be maintained. If the body retains more nitrogen than it gives off, it must be accumulating protein; if it retains more carbon than is given off, it must be storing glycogen or fat, and in either case the body must increase in weight. But whether or not the body may be losing or gaining fat, giving off more or less carbon than it receives, as long as the expenditure of the nitrogen is exactly equal to the income, then the body is said to be in *nitrogenous equilibrium.*

A starving animal or a fever patient, entirely or in part, live upon their own body tissues and are losing nitrogen. A growing child increases its store of nitrogen. In neither case is there nitrogen equilibrium. An animal in starvation excretes kreatinin, urea, and other nitrogenous substances and gives off carbon dioxide, but all expenditures are reduced to a minimum. When its weight has fallen from 25 to 50 per cent., it dies. Muscles suffer most absolutely, and fats most relatively while organs in continuous activity, like the heart and central nervous system, lose practically nothing. During the first day of starvation the excretion of urea is not altered, since it requires about twenty-four hours for the elimination of the protein of the last meal. The excretion of urea then rapidly sinks to a low, constant amount, which is maintained until a short time before death, when there may be either a rapid decline or a brief premortal increase. The duration of starvation depends upon the reserve store of material which the animal possessed. Fats, for instance, economize the proteins of a starving animal, but however much fat there may be, the steady loss of tissue protein goes on. If sugar or sugar and fat are given, the premortal rise in urea excretion does not take place, and the excretion of nitrogen may be reduced to one-third of the amount when no food at all is given. In this way the daily excretion of nitrogen in man has been reduced to four grams. Fat and carbohydrate are much more effective in sparing protein than is fat alone. This is because living matter needs sugar, and when not supplied protein is destroyed to furnish it.

If having determined the daily nitrogen loss in an animal during starvation it be fed with an amount of protein equivalent to this loss, then nitrogen equilibrium would by no means be established. The nitrogen excretion would be nearly double the starvation excretion, and with a progressive increase of food protein the excretion of nitrogen would become greater, but at a diminishing rate, until finally nitrogenous equilibrium is established with an excretion of nitrogen, say three times as much as the starvation excretion. The amount of protein food necessary for nitrogen equilibrium depends upon the condition of the organism—a muscular, well-nourished body requiring more. Having established nitrogen equilibrium, every increase in food protein leads to an increase of nitrogen excretion, but also to some laying on of flesh until nitrogen equilibrium is again established at some higher level.

If, at any level of nitrogen equilibrium, fat be added to the diet, it will be found possible to maintain equilibrium with a much reduced amount of protein food. The fat economizes, to a certain extent, the protein destroyed. On the other hand, when protein in large quantities is given to a fat animal the destruction of fat is accelerated. In the *Banting cure* for corpulence the patient is put upon a diet containing much protein, but little fat or carbohydrate. Carbohydrates are even more effective than fats in economizing protein, and carbohydrates economize fats as well. Albuminoids, like gelatin, are still more effective as protein sparers, but will not act as substitutes for protein. Their value is much like that of carbohydrates, but, owing to their furnishing certain valuable "building stones," more effective. There has been much speculation as to the reason for the inability of gelatin to maintain an animal. It contains most of the amino-acids of protein, but lacks tyrosin, tryptophan, and cystin. It has been claimed that nitrogen equilibrium has been maintained upon a diet of gelatin to which the above amino-acids, plus carbohydrates and fats, were added. Nitrogen equilibrium has been maintained upon the products of pancreatic digestion of casein. But when casein is hydrolyzed with hydrochloric acid this is no longer possible, owing, perhaps, to the too thorough breaking up of the polypeptids.

Within those limits in which, in a normal adult, nitrogenous

equilibrium holds, an animal uses up all the protein that is supplied. During starvation its use of protein becomes extremely economical. A liberal supply of protein given to a starving animal leads at once to an almost entire destruction of the protein. For a time some nitrogen is stored up in the body, but the demand soon becomes equal to the supply. This leads to a generalization: *Destruction of protein is mainly determined by the supply in the food.* This fact, thus expressed, has its *raison d'être* in exogenous metabolism. A large part of the nitrogen of the food passes by way of the liver, as a short cut, to urea and is excreted. This process, while not depriving protein food of its energy value to any great extent, does lead to the preparation of a pabulum for tissue cells, freed from superfluous nitrogen and containing, very likely, those amino-acids in proper proportions suitable for the construction of living substance. The relative small and constant amount of endogenous metabolism indicates that the actual protoplasmic substance is comparatively stable, and that only a small amount of the decomposition products of protein is necessary to supply the waste. Experimentally, this has been shown to be true whether the animal is at rest or not, and there has, as a consequence, been established a second generalization, which may be stated thus: *Within normal limits nitrogenous metabolism is nearly independent of muscular work.* For example, muscular work has little or no effect on the excretion of urea.

The energy for muscular work has its source mainly in non-nitrogenous material. This was first made clear by two experimenters, who, in climbing a mountain on a non-nitrogenous diet, proved that the heat liberated was twice as great as could possibly have come from broken-down protein, estimated from the urea excretion during, and for some time after, the climb. On the assumption that the urea excreted was an adequate indication of the amount of protein broken down, it was evident that a large fraction of the energy must have come from the non-nitrogenous diet. This is corroborated by the very great increase in carbon dioxide elimination which takes place during muscular work. Excessive work in man does cause an increase in nitrogen elimination which comes on rather slowly and lingers for a day or two after cessation

of work. Urea, ammonia, and kreatinin are increased, and if the subject is in poor training the uric acid and purin bases also.

Carbon Equilibrium.—The condition of carbon equilibrium is of lesser importance and less easily attained than nitrogen equilibrium. A normal adult of constant weight is in carbon equilibrium, and when the quantity of non-nitrogenous food is increased there is a greater tendency for it to be stored and not so great a tendency toward its destruction. Carbon equilibrium may be attained on an exclusively protein diet. For a man of 70 kilos, the daily excretion of carbon on an ordinary diet is 250 to 300 grams. About 2000 grams of lean meat would be necessary to yield the same amount of carbon, necessitating the destruction of three times the ordinary quantity of protein in the short cut to urea through the liver. Individuals differ greatly in the ease with which they store carbon. Some, upon a relatively small diet, form much fat, and others remain thin in spite of the ingestion of a very liberal diet. The reason for the difference depends upon the capacity of the body to destroy food material. Within limits this is affected by the character of the daily life. Sedentary work absence of worry, etc., tend to the accumulation of fat, while a very muscular life has the opposite effect. Alcohol, long continued, by sparing carbohydrates and fats and by depressing the oxidative power of the body tends toward the accumulation of fat.

History of Inorganic Salts.—These, in general, do not undergo any decomposition in the body. An exception is to be found in the chlorides, some of which are used in the formation of the hydrochloric acid of the gastric juice. The average amount of the inorganic constituents of the body, determined as ash after incineration, is 4.3 to 4.4 per cent. Five-sixths of this is derived from the bones. Muscle contains from 0.6 to 0.8 per cent. of the moist weight. The more important salts are the chlorides, phosphates, sulphates, carbonates, fluorides, and silicates of potassium, sodium, calcium, magnesium, and iron. Iodine is found in the thyroid tissues. Potassium belongs, especially, to organized tissue elements, while sodium belongs to the liquids more particularly. Calcium carbonate and phosphate predominate in the bones.

The salts are of no importance from an energy point of view. They maintain the normal composition and osmotic pressure in the liquids and tissues of the body. Furthermore, they are in some way bound up in the structure of the living material, so that they are necessary to its normal reactions. They are even found in proteins, and their removal changes the properties of proteins, so that ash-free native proteins are not coagulable by heat and globulins are precipitated. Calcium plays a special part in the coagulation of blood and milk and in the contractions of cardiac tissue. Iron salts are necessary for the production of hemoglobin. Sodium chloride is the only salt that is consciously added to the diet. The average man ingests from ten to twenty grams per diem. The need of sodium chloride is felt by those animals that live on vegetable food. The explanation given for this is as follows: Most vegetables contain a large amount of potassium salts. When these enter the body they react with sodium chloride, forming by their reaction salts foreign to the blood, which are promptly excreted by the kidneys. As a result, the normal percentage of sodium chloride is lessened.

During starvation the body clings to its salts; the amount of sodium chloride excreted soon falls to a low figure (0.6 gram). If ingested in superabundance it is promptly excreted. Calcium salts play an important part in the growth of the skeleton. When dogs are given a calcium-free diet they fall into a condition resembling rickets in children. While most of the calcium passes through the body, undergoing no change, a portion must be involved in the tissue metabolism. Calcium is constantly being eliminated from the inner surface of the intestine in small amount, perhaps 0.15 to 0.16 gram per day. The deposition of calcium increases with age in the arteries, so that they lose their elasticity. Under pathological conditions it may give rise to arterial sclerosis and senile cataract. Milk is a food which is rich in calcium and phosphorus, evidently related to the needs of the developing child. The calcium is in the form of an organic combination, united with proteins as in caseinogen. It is more easily assimilated in the body in this form. The same is true of iron. In ordinary dietaries the iron amounts to only 8 to 10 milligrams per day. A daily excretion takes place through the walls of the intestine. No

doubt it is used over and over again. Milk is poor in iron, so that if the child is weaned too late it is apt to become anemic, and then the milk should be supplemented with food, like the yolk of egg, which is rich in iron. The yolk of egg contains an iron-holding nucleo-albumin called hematogen.

Body Equilibrium.—Just as it is possible to speak of nitrogen or carbon equilibrium, it is possible to speak of water equilibrium, oxygen and hydrogen equilibrium, salts equilibrium, etc. An adult under normal conditions lives so that his ingesta are balanced by corresponding excretions; he is in general body equilibrium and maintains a practically constant body weight. If an exact balance is drawn between proteins, fats, and carbohydrates eaten and those destroyed in the body and represented by the nitrogen and carbon in the excreta, we have a complete balance experiment. In determining protein metabolism the nitrogen of the excreta is multiplied by 6.25. The figure 6.25 is obtained from the proportion, protein molecule : nitrogen contained : : 100 : 16. That is, the nitrogen in the protein forms about 16 per cent. of the molecule by weight.

When, in addition to the determination of nitrogen, the total quantity of carbon metabolism is desired, it is necessary to place the individual in a specially constructed chamber, or respiration apparatus, through which air is drawn by means of a pump. The total quantity of air passing through is measured by a gasometer, and from time to time definite fractions of air are drawn off and analyzed for carbon dioxide. Knowing the total nitrogen and carbon eliminated, it is possible to estimate the amount of protein, carbohydrate, and fat destroyed in the body. A further refinement of this method has led to the construction of respiration chambers in which the income and outgo of energy are determined as well as the material income and outgo. Such chambers act as calorimeters, so that the total heat given off can be determined. The heat value of the diet being known, it is possible to determine whether or not the theoretical amount of heat is actually given off from the body.

Dietetics.—This subject treats of the proper nourishment of individuals or collections of individuals in health and in sickness. The facts may be derived by study along two

general lines: (1) A consideration of the dietaries of various groups of people; (2) by special experiments on man. By the first method Voit concluded that an average workman of 70 to 75 kilos, working ten hours a day, required in twenty-four hours 118 grams of protein, 56 grams of fat, and 500 grams of carbohydrate. The very many figures obtained by numerous experimenters vary within considerable limits, Chittenden, for instance, having recently determined that the average man eats at least twice as much protein as he really requires. Although there are peoples and animals who for long periods of time may live on a diet of flesh alone, it has been found, both by experience and experiment, that for civilized man a mixture of the three main foodstuffs is necessary for health. From a physiological point of view, for a man of 70 kilos the following may be put down as the solids of a normal daily diet: 95 grams of proteins, 80 grams of fat, 310 grams of carbohydrates, and 30 grams of salts. Knowing, as the result of analysis, the composition of various foods, a selection of foods can be made giving the proper proportions of foodstuffs. The protein and carbohydrate should be present in such amounts that there is one part of nitrogen for every fifteen parts of carbon. Oatmeal and wheat flour contain nearly the proper proportions.

A growing child needs, relative to weight, far more food than does a man. In the first place, it requires more food because it is growing. In the second place, the expenditure of an organism is determined by the surface rather than by mass. Roughly, when the weight is doubled the surface becomes only one and one-half times as great. During the first seven months an infant should receive nothing but milk, for careful observations on the carbon dioxide and nitrogen excreted by a child have shown that the assimilation of milk is very complete, 91 per cent. of the total energy being utilized. In an adult maintaining nitrogen equilibrium on milk, only 84 per cent. of the energy is utilized. Human milk contains about 2 per cent. of protein, 3 per cent. of fat, 5 or 6 per cent. of carbohydrate and from 0.2 to 0.3 per cent. of salts. Cow's milk contains about 4 per cent. of protein, 4 to 6 per cent. of fat, 4 per cent. of lactose, and 0.7 per cent. salts. When cow's

milk is given to infants it should be diluted with water and some sugar added to it.

Accessory Articles of Diet.—These include condiments, flavors, and stimulants. They are usually taken in order to make food more attractive. Flavors and condiments stimulate the psychical secretion. Dogs, it has been said, will refuse to eat food which has been entirely deprived of its flavor and sapidity, and would rather starve. When fed on a diet of ash-free fats and carbohydrates, and meats extracted with water until the salts were much reduced, they were in a moribund condition at the end of thirty-six days. Some of the salts, at least, must be in organic combination. Mice will live well on a diet of dried cow's milk, but if fed on the organic but ash-free constituents of milk, namely, sugar, fat, and casein, together with the extracted salts of cow's milk, they died in thirty days.

Stimulants include alcohol, tea, coffee, chocolate, and meat extracts. The value of the latter lies in the possession of secretagogues that stimulate the gastric glands. The stimulating power of all the stimulants mentioned, except alcohol, depends upon xanthin and its derivatives. Alcohol as an article of diet has aroused tremendous controversy, owing to the disastrous results often following its consumption. The main physiological aspects may be summed up as follows:

1. To a certain very slight extent alcohol is a food. It has been proved that it may save protein from decomposition just as carbohydrates and fats do. A small portion is excreted unchanged in the urine and breath.

2. There is no reason to suppose that the energy of alcohol may not be used as a source of work in the body. It yields heat, but ordinarily, owing to the production simultaneously of a cutaneous dilatation, more heat is lost from the body than is gained.

3. A certain amount of alcohol seems to be formed normally in the metabolism of sugar. Nevertheless, there seems to be no use in deliberately adding to this amount in healthy individuals. In all hazardous undertakings it should be avoided.

4. It is no doubt of great value medicinally when its administration is controlled by a physician.

5. In strictly moderate doses (one and one-half ounces of absolute alcohol in twenty-four hours), properly diluted

and taken with food, it is not harmful to healthy average men working under ordinary conditions. Every stimulant may be abused by overindulgence. A special danger in alcohol lies in the acquisition of an alcohol habit. Finally, it must be remembered that alcohol is a depressant rather than a stimulant, from a pharmacological point of view.

QUESTIONS ON CHAPTER VIII

How do absorbed digestion products reach the tissue cells?

Define "conservation of energy."

Does the law of the conservation of energy hold true for the body?

What is the source of energy of the body?

Into what forms of energy does the body convert the energy of the foods?

How much heat is given off by the body per day?

Define a calorie.

Discuss the "combustion equivalent" of foods.

How is the combustion equivalent obtained?

What are direct and indirect calorimetry?

What is the purpose of the decomposition of the protein molecule?

Discuss exogenous and endogenous protein metabolism.

What is the significance of serum-albumin and serum-globulin.

Discuss the formation of urea.

Discuss the formation of uric acid.

Discuss the formation of hippuric acid.

Discuss the formation of kreatinin.

What are the main facts of carbohydrate metabolism?

What foodstuffs are the source of glycogen?

Describe in detail the history of dextrose.

Give a practical test for incipient diabetes.

Describe an experiment showing the relation of the pancreas to the destruction of sugar in the body.

Give the main facts in the metabolism of fats.

What is meant by autolysis?

What is the composition of the urine?

Define nitrogen equilibrium. Discuss.

What changes take place in nitrogen excretion during starvation?

Describe the effect of a protein diet upon nitrogen excretion during a period of starvation.

What are protein sparers?

What is the manner of action of the Banting cure for corpulence?

What reason has been assigned for the inability of albuminoids to take the place of proteins?

Why does the destruction of protein depend mainly upon the supply in the food?

What effect has muscular work on nitrogen excretion?

How is carbon equilibrium determined?

Give the history of inorganic salts in the body.

What values have water and salts to the animal?

What salt especially undergoes a change in the body?

Why do herbivora crave salts?

What are the sources of the salts of the body?

What are the uses of calcium salts?

What is meant by body equilibrium?

How is the amount of protein broken down by an animal determined?

What are respiration calorimeters used for?

What forms the subject matter of dietetics?

Discuss the quantities of foodstuffs necessary per day for an average individual.

Discuss the diet required by a growing child.

Contrast the composition of human milk with cow's milk.

What are accessory articles of diet?

Discuss the physiological aspects of alcohol.

CHAPTER IX

ANIMAL HEAT

WARM-BLOODED and cold-blooded animals are respectively designated as *homoiothermous* and *poikilothermous*. The former have a body temperature that varies very little from a certain normal which is characteristic for the species, while the temperature of the latter varies directly with the medium in which they live, although usually from a fraction to several degrees higher. Man is warm blooded—the *normal temperature* being about 98.5° F. (36.87° C.). The temperature is not invariable, and in the internal organs may be as high as 100° F. under normal conditions. In the rectum the temperature is about 1° F. higher than in the mouth or armpit. The warmest blood in the body is that coming from the liver during digestion, and the coolest is that coming from exposed parts, such as the tips of the ears and the nose. In health the temperature varies slightly with the external temperature, age, exercise, sex, constitution, etc. The temperature of a newborn child is about 37.86° C. *In the adult there is a diurnal variation of 1° to 1.5° F.; being lowest in the morning and highest late in the afternoon.* This corresponds to the usual temperature ranges in fever. In ordinary pathological conditions the temperature does not remain long at a point below 95° F. nor above 105° F. without fatal results. Under conditions of prolonged exposure to cold and the algid stage of cholera, recovery has occurred after a bodily temperature as low as 75° F. On the other hand, in some cases of extreme fever, as from sunstroke, recovery has been noted after a temperature of 110° to 112° F.

It has been proved that the source of animal heat is the potential energy of the *foods*. The latter is converted into heat either directly as the result of chemical decompositions, or indirectly through muscular movements, friction, etc. About 90 per cent. is formed directly. The heat liberated by

an animal may be measured by calculating the potential energy from the food ingested or from the amounts of oxygen absorbed and carbon dioxide given off. This is *indirect calorimetry*. *Direct calorimetry* consists in measuring the heat directly by means of a calorimeter. A calorimeter is an apparatus by means of which the amount of heat given off by an animal may be measured. It usually consists of two concentric cases separated by ice, air, or water, and provided with thermometers and gasometers so arranged as to insure proper ventilation to the animal which is placed in the inner case. The object of calorimetry is to determine the quantity of heat that is dissipated in a definite time. A certain amount of the heat is taken up by the apparatus, some is given to the air that passes through the calorimeter, and finally some is lost in the evaporation of water.

To determine the amount imparted to the apparatus, it is necessary before using to determine its *calorimetric equivalent*, which is done by burning alcohol within it until the temperature has been raised 1° C. One gram of alcohol will yield about 7000 calories of heat, so that if 5 grams of alcohol are required to raise the temperature of the calorimeter 1° C., then the quantity of heat absorbed would be equal to 5 times 7000, or 35,000 calories. This is the calorimetric equivalent. If an animal has raised the temperature of the calorimeter 10° C., the quantity of heat that it has given off would be equal to 10 times the calorimetric equivalent, or to 350 kilogram degrees. The quantity of heat given to the air is determined by measuring the amount of air passing through the calorimeter, and its temperature on its entrance and exit. The volume of the air must be corrected for the increased temperature and then reduced to weight, after which it is multiplied by the specific heat of air at 0° C., and then by the number of degrees of the increase of temperature. By *specific heat* is meant the heat required to raise the temperature of any substance 1° C., and is usually compared to water as a standard. The specific heat of the animal body is about 0.8. The formula for the correction of the volume of air is:

$$V = \frac{V' P}{760 \ (1 + 0.003665t)}.$$

V' is the observed volume; V, desired volume at 0° C. and 760 mm. Hg; P, observed pressure; and t, mean temperature. The value of 760 $(1 + 0.003665)$ is obtained from standard tables. A liter of dry air at 0° C. weighs 0.001293 kilogram.

The measurement of the aqueous vapor of the air before entering and after leaving the calorimeter gives the data for the estimation of the heat lost through evaporation. If it is found that the total quantity of water evaporated from the animal is 100 grams, it is only necessary to multiply by 582 (since it requires this number of calories to evaporate 1 gram of water) in order to obtain the heat in kilogram degrees that is lost by evaporation. The principal part of the total heat produced by the body is generated by muscular activity. Subsidiary sources are the chemical action going on during digestion, friction of muscles, blood, warm foods, sun's rays, etc.

Throughout life the body maintains a constant temperature, so that there is a regulation of heat produced and heat dissipated. The production of heat is known technically as *thermogenesis;* the dissipation of heat, as *thermolysis;* and the regulation of the relations between them, as *thermotaxis.* It is evident that if thermogenesis and thermolysis vary together, the body temperature will remain unchanged; but an increase in thermogenesis with a constant or decreased thermolysis will raise the body temperature. Further, a decrease in thermogenesis with constant or increased thermolysis will lower the body temperature. The production of heat probably takes place in all the tissues of the body, since they all undergo oxidative changes; but the muscles are the main source of the heat not only when active, but when at rest. During activity the greater part of their chemical energy is liberated as heat, only one-fifth appearing as mechanical energy. The work of the heart is entirely converted to heat, forming less than 5 per cent. of the total amount produced in the body. It is known that when a muscle is separated from the central nervous system it continues to produce heat, but much less than before. *Specific thermogenic fibers* have not been isolated. It has been claimed that the act of *shivering* has as its only purpose the production of heat, so that if the muscular contractions of shivering are brought about by impulses passing over ordinary motor nerves, they must have a specific thermogenic function. The follow-

ing facts are suggestive: A rabbit paralyzed by large doses of curare is no longer able to maintain its temperature. It behaves like a cold-blooded animal. The same result is obtained by section of all the motor nerves or, what is the equivalent, section of the cord in the cervical region. In a normal fasting guinea-pig the body temperature remained constant while raising the outside temperature from 0° to 35° C., but the oxidations as determined by the calorimeter were twice as great at the lower temperature. The regulation of heat production by the outside cold is a chemical regulation. By voluntary muscular contractions man possesses a certain mean of counteracting the effect of outside cold. Another method of increasing heat production lies in an increase in the food ingested, since most of the material of the daily diet is promptly burned by the body. Thermogenesis in this case is not strictly voluntary. The appetite stimulated either by exercise or by outside cold leads to an increase in the food eaten.

Thermolysis is brought about by the following agencies:

1. Through the various excreta, urine, feces, etc., which are at the temperature of the body when voided. This loss equals 1.8 per cent. of the total.

2. Through expired air in the warming of the air and in the vaporization of water from the lungs. This loss equals 10.7 per cent. of the total.

3. By evaporation from the skin, equal to about 14.5 per cent. of the total.

4. By radiation and conduction from the skin. By this means 73 per cent. of the total heat of the body is lost. Loss of heat in man is controlled chiefly by varying the amount of clothing which determines the amount of evaporation and radiation from the skin. A more important means of controlling heat loss exists in the reflex control through sweat nerves and vasomotor nerves. This method is a physical regulation. Warm weather induces the secretion of sweat through a reflex stimulation of the nerves supplying sweat glands. The greater quantity of water for evaporation from the skin the greater will be the heat loss. A similar reflex mechanism brings about a vasodilatation of the skin vessels. Cold, on the other hand, causes a vasoconstriction. Finally, the acceleration of respiration which occurs in some animals, especially in dogs, with

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increase of temperature, aids materially in reducing the body temperature.

Heat Centres.—The very many experiments that have been made with the object in view of demonstrating the existence of a special set of heat nerves and heat centres, separate in their action from motor and secretory nerves, are inconclusive. But many significant facts have been brought to light. It has been found that puncture of the brain at the junction of the medulla and the pons causes an increase in heat production. Section of the cord in the cervical region is followed by a fall in body temperature. These facts have been interpreted to mean that there exists in the brain anterior to the medulla a general heat centre which constantly keeps in check heat-producing centres located in the cord. Another important fact is shown by the experiment of the "heat puncture" in which a probe, inserted into the corpus striatum of a rabbit causes a rise in temperature which may last for a long time, although the animal shows no other effects from the operation. There is a difference of opinion as to whether the increased production of heat occurs mainly in the liver or in the muscles. Other heat centres have been located in the optic thalamus septum lucidum, cortex, etc. Much work has been done in the hope of throwing light on the causation of fevers.

Fever.—A fever is a pathological process generally caused by the poisonous products of bacteria and which is characterized by a rise in temperature above the normal. It has been supposed that the action of the bacterial poisons is on the heat centres, and in favor of this view it has been stated that if the basal ganglia are cut off by section of the pons from lower nervous connections fever is no longer produced by injection of bacterial poisons. In conformity with this it is found that antipyrin has no longer any influence on the temperature of the animal. But while it is quite certain that some fever-producing agents (cocaine) act through the central nervous system, it is quite possible that others affect the tissues directly. Likewise, some antipyretics (quinine) act upon heat-forming tissues while others (antipyrin) work indirectly through the nervous system. Fever is always accompanied by other changes than the temperature changes of the body. It is associated with an increased rate of heart beat and respiration. There is a diminution in the alkalies and carbon dioxide of the blood.

The total excretion of nitrogen is increased and there is an alteration in the distribution of nitrogen among the urinary constituents. The ammonia, the uric acid, and the kreatinin are increased while the urea is relatively decreased. Kreatin may also make its appearance.

During the first stage of fever, while the temperature is rising, there is always an increased retention of heat. In most cases the production of heat is also increased on an average from 20 to 30 per cent. Evidence has been obtained that at this stage the cutaneous vessels are constricted. It is most probable that an increased and perverted metabolism is the primary cause of the increased production of heat. Mandel has shown that one of the purin bases (xanthin) causes fever in monkeys, and that the purin bases in the urine are increased both in infective and aseptic fevers. There is a constant relation between the height of the fever and the quantity of purin bases excreted. Xanthin fever can be antagonized by salicylates but not by antipyrin.

QUESTIONS ON CHAPTER IX

Define the terms homoiothermous and poikilothermous.
Give the body temperature of man.
In what ways does it vary?
Where are the warmest and the coldest blood of the body to be found?
What factors influence body temperature?
What is the source of the energy of heat?
What percentage of heat is directly formed from the chemical energy of the food?
What are direct and indirect calorimetry?
Describe a calorimeter.
Describe fully how the calorimetric equivalent is obtained.
Why is it necessary to obtain the calorimetric equivalent in calorimetry?
Explain in detail how the heat lost to the air is calculated.
What is the specific heat of a body?
Explain how the heat lost by evaporation of water is obtained.
What organs are principally concerned in heat production?
What subsidiary sources of heat are there?
How much heat does the heart produce?
Define thermogenesis, thermolysis, and thermotaxis.
Discuss thermotaxis.
What is the effect upon heat production when a muscle is separated from the central nervous system?
Discuss the phenomenon of shivering.
What is the proof that thermogenic centres exist?
What classes of thermogenic centres are there, and where are they located?
How is thermolysis brought about?
Explain the postmortem rise of temperature.
Discuss the chemical and physical regulation of body temperature.
Discuss briefly the physiological aspects of fever.

CHAPTER X

SPECIAL MUSCULAR MECHANISMS

Mastication.—The teeth of different varieties of mammalia are adapted to the work which they have to perform. In herbivora they serve to grind the food; in carnivora to tear and cut the food; and in man, omnivorous, they are adapted to serve both grinding and cutting purposes. In man there appear in succession two sets of teeth. The first set are temporary and consist of twenty teeth—four incisors, two canines, and four molars on each side. They appear in order—central incisors at the seventh month after birth, the other incisors at the ninth month, the canines at the eighteenth month and the molars at the twelfth and twenty-fourth months respectively. The teeth in the lower jaw appear a little before the corresponding ones of the upper jaw. The second set of teeth or permanent set begin to replace the temporary set between the sixth and seventh years. There appear, in addition, twelve true molars, making the total number of teeth thirty-two. The wisdom teeth appear about the twenty-fifth year.

In order that the food may readily be swallowed and acted upon by the digestive juices it is finely divided by the action of the jaws, which, by means of the incisors and canines, cut the food, and by means of the bicuspids and molars, crush it. The lower jaw is raised by the masseter, temporal, and internal pterygoid muscles; depression is largely passive, but is aided by the digastrics and slightly by the mylohyoid and geniohyoid muscles. When the infrahyoid group fix the hyoid bone, all the muscles passing between it and the mandible act to depress the latter; it is moved laterally by the external pterygoids acting separately, and forward by their joint action, and is retracted by the horizontal fibers of the temporals. The action is voluntary, the impulses coming through the trigeminal and hypo-

glossal nerves. The tongue and cheeks serve to bring and keep the food between the teeth.

Deglutition.—Swallowing begins as a voluntary act and insensibly becomes an involuntary reflex. The voluntary part of the swallowing consists in the manipulation of the bolus of food so that it lies on the upper surface of the tongue. The anterior part of the tongue is then elevated against the hard palate. The elevation travels backward with considerable pressure from tip of tongue to the base, when a sudden sharp contraction of the mylohyoids places the bolus under such pressure that it is shot backward through the isthmus of the fauces and into or through the pharynx. Simultaneously with the passage of the food through the pharynx a large number of muscles by their coördinated contractions have closed off the openings from mouth to posterior nares and to the larynx. The levator palati and tensor palati muscles have raised the soft palate; at the same time the contraction of the superior constrictor has brought the posterior wall of the pharynx forward to meet the soft palate. The soft palate, the uvula and the posterior wall of the pharynx form, together, a sloping surface which completely closes the pharynx from the posterior nares.

Immediately after the contraction of the mylohyoids the larynx is pulled upward and forward by the contraction of the thyrohyoid muscle and by the elevation of the hyoid bone. The base of the tongue is at the same time drawn backward by the stylo- and palatoglossus. The epiglottis is thus caused to come into contact with the orifice of the larynx. The glottis is also closed by the approximation of the vocal cords, brought about by the contraction of the lateral cricoarytenoid muscles. That the epiglottis is not absolutely necessary to swallowing has been determined by surgical procedures.

A bolus of food, if of same size and consistency, is now grasped by the constrictors of the pharynx and moved into the esophagus, along which it is carried by peristalsis. Peristalsis consists of a constricting wave preceded by a wave of inhibition. In conformity with the character of the muscle tissue found in the wall of the esophagus, peristalsis moves more rapidly in the upper than in the lower portion. In man the peristaltic wave reaches the cardiac sphincter guarding

the opening of the stomach, in five or six seconds after the contraction of the mylohyoid muscle. Of this total time only one-tenth second is spent by the food in the pharynx. The arrival of the food at the cardiac sphincter causes an inhibition of the tone of the sphincter so that the swallowed food may be passed into the stomach. In the case of liquid food the passage of the esophagus is accomplished more quickly. Such food is thrown or shot down into the lax esophagus to a varying distance. The slight contraction of the diaphragm just before deglutition sets in has the effect of placing the esophagus under diminished pressure and perhaps of straightening it somewhat, both events facilitating the passage of the food. The normal peristaltic wave follows later, gathering together, as may be imagined, remnants clinging to the esophageal wall and ultimately moves the whole mass into the stomach, an event which may be appreciated by auscultation at the lower end of the sternum.

The peristalsis of the esophagus is of interest on account of its close connection with the central nervous system. The ligation, crushing or even section of the esophagus does not interfere with the passage of the wave. Even when removed from the body under proper conditions the esophagus continues to manifest its peristalsis. Ordinarily, stimulation of the mucous membrane of the pharynx causes movements of the esophagus while stimulation of its own mucous membrane is ineffective. These facts are interpreted as follows: That the esophagus possesses the power of peristalsis *per se*, but that this is ordinarily carried out by reflexes having their source in the pharynx at or near the area that also reflexly determines the contraction of the mylohyoid. The term reflex implies a centre, which has been located in the upper portion of the medulla. The deglutition centre is connected with sensory areas of the posterior portion of the tongue, the soft palate, fauces, and tonsils by fibers of the superior laryngeal, pharyngeal branches of the vagus, palatal branches of the fifth and the glossopharyngeal. Stimulation of the central end of the superior laryngeal will cause swallowing movements, but if the central end of the glossopharyngeal is stimulated at the same time the swallowing is inhibited. It is through the mediation of fibers of the ninth nerve that in a series of

successive swallows only the last is followed by an effective peristalsis. The glossopharyngeal also inhibits respiration during deglutition—an inhibition that is effective at any stage of respiration and lasts for four or five seconds. It differs, therefore, from the respiratory stoppage following stimulation of other sensory nerves. Efferent fibers pass to the deglutition mechanism, by way of fibers of the twelfth, tenth, ninth, seventh, and fifth nerves. The vagus has a special relation to the esophagus. Swallowing is interfered with after section, and stimulation of the peripheral end causes movements of the esophagus.

Movements of the Stomach.—From a physiological point of view the stomach is divisible into two parts, the antrum pylori and the fundus. The junction of these two parts is marked, more or less, by a constriction which is the consequence of a tonic contraction of the sphincter of the antrum. The latter is little more than a physiological sphincter. A few minutes after food is ingested a circular contraction, beginning at the transverse band, runs in the direction of the pyloric sphincter. Other constrictions follow and they become more pronounced and energetic, involving the portion of the fundus which lies next to the transverse band. Their direction is always toward the pylorus. Two or three waves may be visible at any one time. The effect upon the food is to drive that portion of the stomach contents lying next to the stomach walls toward the pylorus, and since the pyloric sphincter remains closed there is a regurgitation of food backward through the centre of the advancing wave of constriction. The effect is a churning of the food in the antrum pylori where it gradually becomes mixed with the secretions of the gastric glands. The semiliquid food, called chyme, becomes acid in its reaction and thus becomes the effective stimulus in a reflex inhibition of the pyloric sphincter. With the relaxation of the sphincter a portion of the liquid gastric contents makes its way into the duodenum.

The rapidity with which the passage of chyme from the stomach to the duodenum takes place depends largely upon the nature of the food. Carbohydrates leave the stomach sooner than fats and fats sooner than proteins. The reason for this lies in the quantity of acid formed during the digestion

of these foods. For it has been shown that dilute hydrochloric acid will remain in the stomach longer than water. The acid chyme, when it reaches the duodenum, brings about a reflex tonic contraction of the pyloric sphincter until the acid has been neutralized by the alkaline bile and pancreatic secretion. During the sojourn of the food in the stomach the fundus remains in a state of tonic contraction, so that as the chyme leaves the antrum it is gradually replaced by the contents of the fundus. The peristalsis of the stomach is independent of the nervous system. There is, however, a rich supply of nerve fibers from two sources: From the *vagi* and from the *solar plexus*. Stimulation of the first causes a contraction, and stimulation of the second an inhibition of the stomach. Their function is probably a regulatory one.

Vomiting.—Vomiting is a complex reflex action. It is preceded by a feeling of nausea, a flow of saliva, and retching movements which are brought about by spasmodic contractions of the diaphragm with a closed glottis. This causes the negative pressure in the thorax to increase and open the esophagus, while simultaneously pressure is brought to bear upon the stomach. The abdominal muscles, vigorously contracting, force the contents out of the cardiac end of the stomach and up through the mouth. The glottis is closed, and the nasal passages also. *The stomach during vomiting may not be inactive, but the main factor in the ejection of its contents is the contraction of the abdominal muscles.* This was shown by Magendie, who substituted a bladder of water for the stomach and produced vomiting by injection of an emetic. It has been shown, moreover, that an emetic is without effect in a curarized animal. Vomiting is brought about by local irritation of the mucous membrane of the stomach, by tickling the pharynx, by psychical states, lesions of the brain, by toxic substances in the blood, etc. The *afferent path* when the reflex is from the stomach is through the vagus. A *centre* has been described near the calamus scriptorius, but its existence is not certain. The *efferent impulses* pass over fibers of the vagus, phrenics, and spinal nerves that supply the abdominal muscles.

Movements of the Small Intestine.—The movements of the small intestine are of two or three types. *Peristalsis* is here developed to a high degree. Such movements may pass over

FIG. 8
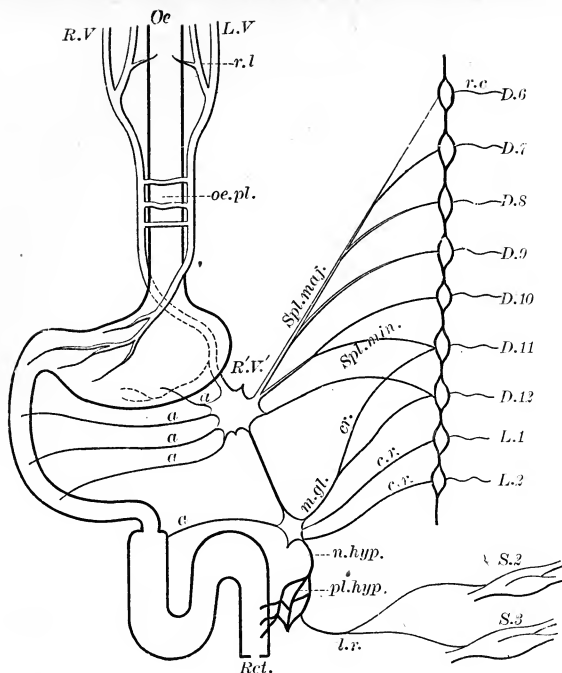
Diagram to illustrate the nerves of the alimentary canal in the dog. (Foster.) The figure is, for the sake of simplicity, made as diagrammatic as possible, *and does not represent the anatomical relations:* Oe. to Rct., the alimentary canal, esophagus, stomach, small intestine, large intestine, rectum; L.V., left vagus nerve, ending on front of stomach; r.l., recurrent laryngeal nerve supplying upper part of esophagus; R.V., right vagus joining left vagus in esophageal plexus, oe.pl., supplying posterior part of stomach and continued as R'.V'. to join the solar plexus, *here represented by a single ganglion* and connected with the inferior mesenteric ganglion (or plexus) m.gl.; a, branches from the solar plexus to stomach and small intestine and from the mesenteric ganglion to the large intestine; Spl.maj., large splanchnic nerve arising from the thoracic ganglia and rami communicantes, r.c., belonging to dorsal nerves from the sixth to the ninth (or tenth); Spl.min., small splanchnic nerve similarly arising from tenth and eleventh dorsal nerves. These both join the solar plexus and thence make their way to the alimentary canal; c.r., nerves from the ganglia, etc., belonging to eleventh and twelfth dorsal and first and second lumbar nerves, proceeding to the inferior mesenteric ganglia (or plexus), m.gl., and thence by the hypogastric nerve, n.hyp., and the hypogastric plexus, pl.hyp., to the circular muscles of the rectum; l.r., nerves from the second and third sacral nerves, S.2, S.3 (nervi erigentes), proceeding by the hypogastric plexus to the longitudinal muscles of the rectum.

the viscus at a rate of 1 mm. per second, and may be excited by mechanical stimulation of the mucous membrane by food or otherwise. Such movements, arising at any point, do not pass the ileocecal valve. Intestinal movements of this kind are intimately dependent upon a definite mechanism within the intestinal wall, for if a portion of the tube be resected, turned about and resutured in its place, peristaltic waves cannot pass the operated area. This mechanism is looked upon as involving Auerbach's plexus, for all progressive peristalses are abolished by poisons like cocaine and nicotine.

A second variety of movement of the small intestine is the *rhythmic type*. Here the intestines, when examined with Röntgen rays, after suitably mixing the food with bismuth subnitrate, may be seen to separate the intestinal contents into a series of segments by circular, stationary constrictions. These segments are in turn divided by other constrictions and the divided halves of neighboring segments fuse together to form a new set of segments. This process, in the cat, is repeated at the rate of 30 per minute. The result is a thorough mixing of the intestinal contents with the intestinal secretions. After possibly a thousand segmentations a peristaltic wave moves the segments to another loop of the intestine, where the rhythmic process is repeated. These movements are differently affected by cocaine and nicotine than are the peristaltic movements. They may even become increased in vigor. They too, however, are also dependent upon Auerbach's plexus, for if the circular muscle coat is stripped off it loses its automaticity while the longitudinal coat still in connection with the plexus retains its spontaneous movements. Under special conditions there may be a reversal of the direction in which the intestinal contents move. This occurs in obstruction of the intestine, and, experimentally, substances introduced into the rectum have later been found in the stomach.

Movements of the Large Intestine.—The musculature in the large intestine has the same general arrangement as in the small and the law of intestinal peristalsis holds as well, *i. e.*, a local excitation causes a constriction above and a dilatation below the point stimulated. A study of the large intestine by means of *x*-rays has shown that it is functionally divisible

into two parts. In the first part (ascending and transverse colon, cecum) the most frequent movement is an *antiperistalsis* which begins somewhere in the colon and passes toward the ileocecal valve. These waves occur in groups, separated by periods of rest. The ileocecal valve prevents the backward passage of food into the small intestine. It requires about two hours, in man, for food to pass from the ileocecal valve to the hepatic flexure and four and one-half hours to reach the splenic flexure. As the colon becomes filled some of the material penetrates the second part of the large intestine, namely, the descending colon. In this part peristaltic waves move the contents toward the rectum.

The intestines have a *double nerve supply*. The fibers of the vagi carry chiefly motor impulses, while those of the sympathetic, chiefly inhibitory impulses. The intestinal movements are not altered by complete severance of all extrinsic fibers, so that the latter probably have only a regulatory influence. It is known the movements may be influenced by psychical states, so that there are evidently connections with higher centres.

Defecation.—When the undigested food has reached the lower part of the large intestine and the rectum, sensory impulses pass to the brain from the latter, giving rise to a desire to defecate. The normal peristaltic movements of the rectum are increased, while voluntarily a deep breath is taken, the glottis is closed, and pressure is brought to bear upon the abdominal contents. The external sphincter ani is voluntarily relaxed, while the internal sphincter is inhibited. Both rectum and sphincters have a double nerve supply, which in function are motor and inhibitory. It has been shown that section of the spinal cord of dogs in the lower thoracic region does not prevent normal defecation. The *centre* probably lies in the lumbar cord, but is connected with the brain so as to be under voluntary control.

Micturition.—The urine as it is formed in the kidney is periodically carried to the bladder by a peristaltic action of the ureters. Whether the peristalsis is due to the stimulus of the contained urine or whether the ureters are automatically rhythmic is not known. The urine is emptied into the bladder in a series of spurts, and is prevented from flowing through

the urethra by the elasticity of the parts and perhaps also by a tonic contraction of the internal sphincter of the bladder. As it increases in amount and a desire to micturate arises, the sphincter of the urethra is voluntarily contracted to prevent the escape of urine, and the back flow through the ureters is prevented by their oblique entrance. Micturition is initiated voluntarily by a relaxation of the sphincter urethræ. The walls of the bladder contract, driving the liquid out forcibly. This may be aided by a closure of the glottis and a contraction of the abdominal muscles. In the male the last portions are ejected in spurts by the contractions of the bulbocavernosus muscle. The *tone* of the bladder is continually undergoing changes, so that the pressure of the urine varies independently of the quantity present. This explains why a desire to micturate, if not satisfied, may pass off. The *centre* of micturition has been located in the lumbar portion of the cord, between the second and fifth lumbar spinal nerves. The bladder has a *double nerve supply.*

1. From lumbar nerves passing through the inferior mesenteric ganglion and hypogastric nerves. Stimulation of these causes a feeble contraction.

2. From sacral spinal nerve fibers contained in the nervus erigens. Stimulation of these causes a strong contraction (Fig. 8).

Parturition.—This process is inaugurated by painless, rhythmical peristaltic waves that sweep over the upper segment of the uterus. These contractions increase in intensity and duration until they give pain, which is intensified by resistance ahead or may be absent altogether if the child is small and the canal large and free. The pain is at first confined to the uterus, but later spreads up into the abdomen and down into the thighs. Contractions in the human being involve only the upper portions of the uterus, the lower segment and cervix remaining passive. When the membrane which precedes the fetus in its passage through the os uteri bursts, there is for a time a cessation of uterine contractions (owing to the considerable reduction in the bulk of the uterine contents), but they are soon renewed with increased vigor, aided by forcible contractions of the abdominal muscles and by forcible expirations with closed glottis. By these means the head of the fetus is

gradually pushed through the os into the vagina, followed by the more easily passing remainder of the body. After expulsion of the fetus the contractions gradually diminish, becoming painless, and in about fifteen minutes the after-birth, consisting of placenta, amnion, chorion, decidua reflexa, and parts of the decidua vera appears. At this time the blood flows freely; the average loss, amounting to about 400 grams, which can be and should be greatly reduced by a proper "following down"—*i. e.*, intermittent massage—of the fundus. After parturition, by a process of involution lasting for several weeks, the uterus returns to its unimpregnated state. The entire process is a *reflex* act, the nervous *centre* being in the lumbar portion of the cord. The nerves reach the uterus in company with bloodvessels, and are derived from the pelvic plexus.

Locomotor Mechanisms.—The two hundred or more bones of the body are joined together to form articulations of four types: *Sutures, symphyses, syndesmoses,* and *diarthroses*.

A *suture* is formed when two bones gradually interlock immovably, leaving only a more or less distinct seam. The best examples are in the skull.

A *symphysis* is the union of two bones by fibrocartilage, as in the case of vertebræ. This allows a limited amount of movement.

A *syndesmosis* is a union of two bones by fibrous bands, which allows considerable movement as in the inferior tibiofibular articulation.

A *diarthrosis* is a union between two bones that allows the greatest movement, generally, however, only in a special direction. The parts in contact are lined with cartilage, and lubricated with a viscid synovial fluid. The union is made firm by guiding ligaments and fibrous capsules. In some cases, as in the head of the femur and acetabulum, the parts fit so well that they are kept in place, partially, at least, by atmospheric pressure.

The *movements between joints* may be: (1) *Angular;* (2) of *circumduction;* (3) of *rotation;* (4) *gliding.* In the first the angle between the long axis of the bones changes in value. In the second the longitudinal axis of the bone forms the sides of a cone whose apex is at the joint. In the third the bone

moves about its longitudinal axis.   In the fourth, one bone slides over the other.

Many of the bones may be looked upon as levers, with the muscles attached as sources of power.   *Levers* are divided into three classes, according to the relative position of the power, the weight to be moved, and the axis of motion or fulcrum.   Different movements of the foot offer an illustration of the three kinds of levers.   The *first* kind (Fig. 9), where the fulcrum (*F*) is between the source of power (*P*) and the weight or resistance (*W*), is shown when the foot is raised and the toe tapped upon the ground, the ankle-joint being the fulcrum.   The *second* kind of lever, where *W* is between *F* and *P*, is illustrated when the body is raised upon the toes, which, resting upon the ground, are the fulcrum.   The *third* kind of lever, where *P* is between *F* and *W*, is illustrated when a weight is held up by the toes, the ankle being the fulcrum and the anterior group of muscles of the leg the source of power.

FIG. 9

I   II   III
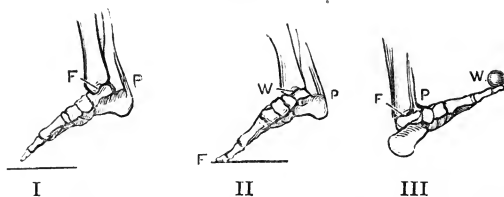
Illustration of levers of all three orders (Huxley): *W*, weight of resistance; *F*, fulcrum; *P*, power.

Standing is a complex coördinated action in which the muscles are continually in play to keep the centre of gravity of the body over the base of support.   In *walking* the centre of gravity is continually being put forward, but the body is kept from falling by the legs, which alternately move forward to sustain it.   One foot or the other is continually on the ground. *Running* differs in that the body is more forcibly moved ahead by vigorous pushes.   The body is more inclined, and both feet leave the ground at times.

Voice.—The *larynx* is a closed cavity, except in its communications with the trachea below and the pharynx above.   The

walls are made up of cartilages, together with various muscles and membranes. Across the cavity in an anteroposterior direction are stretched the *vocal cords,* by the vibration of which the voice is produced. Mere vibration of the cords held in a state of tension by muscular action produces in itself but a feeble sound. This is intensified by *reënforcement* of the vibrations by resonating cavities above and below the cords. It is necessary to consider three features of the voice—the *intensity,* the *pitch,* and the *quality.* The *intensity* depends upon the amplitude of vibrations of the cords. This is partly the result of their structure and partly of the energy with which the air passes between them. The *pitch* is determined by the thickness, tension, and length of the cords. The *quality* of the tone depends upon the character of the upper partial tones which are combined with the fundamental tone. These are varied by altering the shape and size of the buccal and nasal cavities. The voice is controlled by an exceedingly *complex nervous mechanism* of afferent and efferent fibers to various centres in the cerebral cortex. That relations between the hearing and speech centres, for instance, are very intimate is shown by the fact that dumbness is usually a defect of hearing which leaves the voice uncontrolled by the ear in pitch and quality. The pitch of the voice is elevated usually by the contraction of the cricothyroid muscle, which stretches the vocal cords. There are numerous other methods of altering the pitch. Whenever there is a transition from one method to another, a break occurs in the musical scale. The range of voice between these breaks is known as a *register.* The lowest register is commonly designated as the *chest voice,* and the highest as the *head voice.* When a third division is made, it is by some called the *falsetto.* *Speaking* consists of short musical sounds produced by the vocal cords with other noises added by the mouth parts, the whole being interrupted by different methods of obstruction. In *whispering* the musical component is greatly replaced by noisy vibrations.

QUESTIONS ON CHAPTER X

What is the function of the jaws and the teeth?
Tell what you can of the temporary and permanent sets of teeth.
Give action of the muscles concerned in mastication.
What purpose do the tongue and cheeks serve?
Into what stages is deglutition divided?
Describe each stage in detail.
How does the deglutition of liquids differ from that of solids?
How long does it take food to pass from the pharynx to the stomach?
Is swallowing reflex or voluntary?
What is the effect of sectioning the esophagus on peristalsis?
Give the nervous mechanism of deglutition.
Describe the movements of the stomach.
What is the function of the fundic end of the stomach?
Give the nerve supply to the stomach and its function.
Describe vomiting.   Is it a reflex act?
What experiment shows that food is ejected from the stomach mainly
by the contraction of abdominal muscles?
Give the nerves involved in vomiting.
Explain the movements of the intestines.
What is antiperistalsis?
What is the proof that normal peristalsis is due to a nervous mechanism?
What are the differences between the peristaltic and the rhythmic move-
ments of the intestine?
How do rhythmic movements aid the circulation?
Discuss the nervous mechanism of the intestines.
Describe defecation.   Give nerve supply and locate centre.
Describe micturition.
Explain why a desire to micturate may pass off.
Locate centre and give nerve supply involved in micturition.
Describe parturition.
What forms the after-birth?
How much blood is lost during parturition?   Is this essential?
Give source of nerve supply and locate centre involved in parturition.
Name the types of articulations between bones.
Define each type.
What kinds of movements may take place between joints?
Describe the three kinds of levers formed by bones.
Define standing, walking, and running.
How is the voice produced?
Define pitch, intensity, and quality of voice.
What is the relation of the centre of speech to other centres of the cerebral
cortex?
What constitutes a register?
Define head voice, chest voice, and falsetto.
Define speaking.   Define whispering.

CHAPTER XI

MUSCLE AND NERVE

THE phenomena of muscle and nerve can most easily be studied in cold-blooded animals. The frog's gastrocnemius serves this purpose well, and when the sciatic nerve supplying it is carefully left attached, there results a nerve-muscle preparation. If the nerve of such a preparation is in any manner excited, the muscle responds by a sharp and quick contraction or twitch. The excitation of the nerve has given rise to a disturbance of unknown nature in the substance of the nerve, which passes rapidly along its length to the motor end plate and excites the muscle fiber, which responds by exhibiting its most characteristic function, contraction.

Any external influence which can excite living matter to action is an *irritant* or *stimulus*. There are five classes of stimuli—mechanical, thermal, electrical, chemical, and physiological. The quantitative effect which these produce upon living matter depends not only upon their efficiency, but also upon the degree of irritability of the living material upon which they act. The most desirable stimulus for experimental purposes is the electrical current, which produces very little injury and may be finely graded as to strength, time, and place of application. It may be either a constant or induced current. The former, also called voltaic current, is such as is furnished by any cell like a Grove or Daniell. The latter is obtained by the use of an induction coil. This instrument consists essentially of two coils of copper wire, one of which is placed within the other, but *between which there is no metallic connection.* The inner coil of heavy wire (*primary coil*) is connected with a source of electricity, like a cell. The ends of the outer coil (*secondary coil*), which consists of many turns of fine wire carefully insulated, are connected with electrodes, by means of which the induced current is applied to the tissues to be

12

stimulated. Any change in the strength of the *primary current* —*i. e.*, the current furnished by the voltaic cell—brings about a change of potential in the outer coil, which manifests itself as the *induced* or *secondary current*. This gives a strong shock of momentary duration and produces less injury than the voltaic current.

The shock resulting from closure of the primary current is called the *closing shock*, while that from the opening is called the *opening shock*. With the constant current the former is more effective than the latter. The opposite is true of the induced current. The cause of this difference lies in the construction of the induction coil. As the current passes along each turn of wire forming the primary coil it excites an "induced" current in the neighboring turn of wire, which, having an opposite direction to the primary current, opposes it, and therefore delays it in reaching its maximum strength; but, when the primary current is broken, both it and the induced currents in the neighboring turns of wire have the same direction and do not oppose each other. Since the *intensity* of the induced current with the same strength of primary current depends upon the rapidity with which the primary reaches its maximum, it follows that the closing induced current must be weaker than the opening, and have, consequently, a smaller stimulating effect.

The effect of a stimulus is proportional to the *rate* with which it reaches its maximum. This is true only within limits, for a stimulus may be applied both too slowly and too quickly to produce any effect. This has been expressed in Du Bois-Reymond's law: "It is not the absolute value of the current at each instant to which the motor nerve replies by a contraction of its muscle, but the alteration of this value from one moment to another; and, indeed, the excitation to movement which results from this change is greater the more rapidly it occurs by equal amounts, or the greater it is in a given time." This law is not strictly true.

The *denser* the current the greater is its stimulating effect. This is well illustrated by the phenomena of unipolar action. Usually, in order to stimulate a preparation with an electrical current, it is necessary that there shall be a complete circuit; but under certain circumstances one wire of a secondary coil

leading to the nerve is sufficient to excite it when the primary circuit is opened. This may be explained by the assumption of an electrical charge generated in the secondary coil and passing through the nerve to the muscle. In its *transit* through the nerve it arouses a *nerve impulse.* If the electrode represented by the wire on which the nerve rests be replaced by a sheet of gold foil which is made to touch the nerve and muscle along their entire length, the charge from the induction coil will reach all points of the preparation at practically the same instant and will not excite it. The *charge* remains of the same *strength*, but the *electrodes* alter the *density.*

The *duration* of a stimulus must be of sufficient length to produce an effect. *In the experiments of Tesla, where powerful alternating currents are passed through the body without injury, it is the exceedingly small duration of the changes that prevents harmful effects.* It has been found that the results obtained by applying a constant current to a nerve depend upon the *direction* in which the current flows through the preparation.

A current, for instance, which in passing through the nerve from the *anode (positive electrode)* to the *kathode (negative electrode)* flows in the direction of the muscle is called a *descending current;* while one flowing in a direction away from the muscle is an *ascending current.* If a current of such strength is chosen that the closing shocks only are effective, its direction is of no consequence. This is true also when the current is increased in strength, so that both opening and closing shocks are capable of causing the muscle to contract. With a strong current, however, it is found that the closing shock in an ascending current and the opening shock of a descending current cause no contraction. In order to understand these results, it is necessary to consider the changes that a constant current produces in a nerve to which it is applied. These are known as *electrotonic changes*, and they differ in character at the anode and the kathode, so that the condition at the former has been named *anelectrotonus*, while that at the latter electrode is known as *katelectrotonus.* While the current is flowing, the irritability of the nerve is raised at the kathode and is lowered at the anode, and this condition is reversed immediately when the current ceases to flow. An excitation is inseparable from a rise in irritability. The underlying causes of both are the same. It

may be accepted then that the rise of irritability of the nerve at the kathode when the stimulating current is closed, and at the anode when the current is opened, indicate the generation of nerve impulses.

Closing excitations arise at the *kathode*, while *opening excitations* arise at the anode. Moreover, during electrotonus the conductivity is increased slightly at the kathode and decreased greatly at the anode. When the current ceases to flow, the conductivity is greatly lowered at the kathode and is raised

Fig. 10
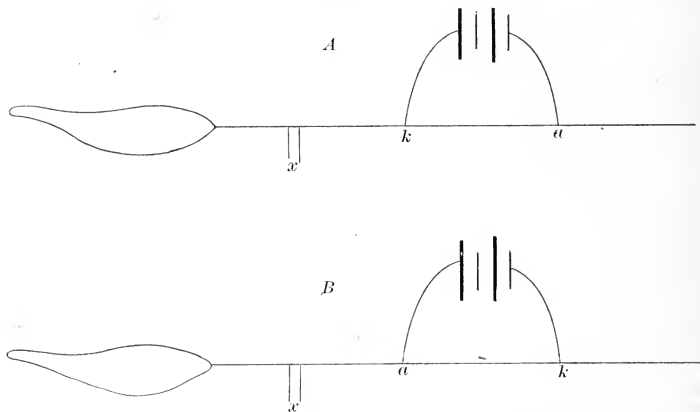
Muscle-nerve preparations: With the nerve exposed in *A* to a *descending* and in *B* to an *ascending* constant current. (Foster.) In each, *a* is the anode, *k* the kathode of the constant current; *x* represents the spot where the induction shocks, used to test the irritability of the nerve, are sent in.

at the anode. Reflection will make clear that with an ascending current the closing contraction fails to appear because the conductivity is so lowered at the region of the anode that the excitation which arises at the kathode cannot reach the muscle. With a descending current the opening contraction fails to appear because the conductivity is so lowered at the kathode that the nerve impulse generated at the anode cannot reach the muscle. The impulses that originate at the electrode nearest the muscle are the only ones that are effective. At

some point between the electrodes the region of increased irritability merges into that of decreased irritability. This point is nearer the anode, but with increase of strength of current it approaches the kathode. The facts relating to the effect of direction of current on the resulting contraction constitute what is known as *Pflüger's law*.

Current strength.	Ascending current.		Descending current.	
	" Make."	" Break."	" Make."	" Break."
Weak current .	Contraction	. . . .	Contraction	
Medium current.	Contraction	Contraction	Contraction	Contraction
Strong current .	. . . .	Contraction	Contraction	

When a nerve intact within the tissues of an animal is subjected to an electrical current it is impossible to prevent the spread of the latter through the surrounding tissues. At the *point* of *entrance* of the current it spreads out brush-like, to be concentrated again at the point of exit. Directly under the physical anode the current enters the nerve, flows through it at varying angles, and so forms in the nerve a physiological anode and kathode. The same thing happens at the point of exit of the current. Therefore, there are four points from which an impulse may be generated. There may be:

1. An *anodic closing contraction*, which is the result of an impulse generated at the *physiological kathode* under the *physical anode*.

2. An *anodic opening contraction*, which is the result of a change developed at the *physiological anode* under the *physical anode*.

3. A *kathodic closing contraction*, which is the result of an impulse generated at the *physiological kathode* under the *physical kathode*.

4. A *kathodic opening contraction*, which is the result of an impulse generated at the *physiological anode* under the *physical kathode*.

These are abbreviated, respectively, ACC, AOC, KCC,

KOC. When the stimulating current is increased gradually in strength, they appear in the following order: KCC, ACC, AOC, and KOC. This order of appearance is explained by three facts:

1. When the current is closed, the impulse is generated at the kathode; and when it is opened, at the physiological anode.

2. The impulse developed at the kathode is more effective than the one developed at the anode.

3. The effect of the current is greatest where the density is greatest.

When nerve and muscle are diseased, the ACC and KOC are obtained respectively with weaker currents than KCC and AOC. This is known as the *reaction of degeneration*. It has been found that when a current is passed through a nerve or muscle at right angles to the direction of its fibers it has no stimulating effect.

The *irritability* of a preparation depends upon changes in its environment and upon changes within itself. Changes of environment include mechanical agencies, temperature, chemical agencies, and electrical currents. Mechanical agencies acting on living substance usually first increase, but later destroy the irritability. In general, cold decreases, while heat increases the irritability, but in this case it is necessary to take into consideration the character of the stimulus employed. Tissues differ normally in their response to various stimuli. A medullated nerve, for instance, responds better to an induced current than to mechanical or chemical stimuli, but the application of cold makes it more susceptible to the effects of mechanical stimulation than to the exceedingly short induced current. Chemicals first raise and then lower the irritability. Deprivation of the blood supply is equivalent to a change in the chemical environment of a tissue. That the normal irritability is dependent upon the blood supply is shown by *Stenson's experiment* on the rabbit, in which the abdominal aorta was closed by compression. The paralysis which follows this procedure is due successively to the loss of function of nerve cells in the cord, then of the motor end plates, and finally of muscle and nerve fibers.

That the irritability of a preparation depends upon changes that may take place within itself is shown by the separation

of a nerve fiber from its cell body, and by the effects of functional activity. The metabolism of a cell depends upon the presence of nuclear matter, so that if a nerve fiber is cut off from its cell body it will degenerate. During this process there is first an increase and then a decrease of irritability. A muscle separated from the central nervous system by section of its motor nerve will also degenerate. After a period of two weeks or so it responds better to stimuli of long duration than to those of short duration, and gradually becomes less and less irritable to the end of the seventh or eighth month. Functional activity leads first to an increase of irritability, but later in this case also to a decrease. This is attributable to both the consumption of its store of nutriment and to the accumulation of waste products. Some physiologists have drawn a distinction between the results of these two processes. Waste products if formed faster than they can be gotten rid of give rise to *fatigue,* while the consumption of stored or available nutriment gives rise to *exhaustion.* That waste products are formed during activity is shown by an experiment of Mosso. Having found the injection of a definite amount of blood from a rested dog into the veins of another to be without effect, he repeated the injection by using the blood of a dog completely tired out by a hard day's work. *The dog receiving the blood showed all the signs of extreme fatigue.*

It is said that in order that protoplasm may conduct, it must be continuous. A break in the physiological continuity of protoplasm, as when a nerve is crushed at one point, completely bars the *conduction process.* The cut ends of the nerve when placed in contact will not transmit a nerve impulse, which distinguishes the latter from an electrical current, which passes readily from one part to the other. A conduction process having reached the boundaries of the cell in which it has originated may cause the generation of a similar process in a contiguous protoplasmic mass. This, for instance, is shown by the relations of the end brush of one cell to the dendrites of another. But fibers of muscles and nerves do not stimulate their neighbors normally as they lie side by side, since their sheaths prevent even contiguity. That the conduction process passes in both directions along the length of the fiber may readily be seen in muscle, where it is accompanied by a change of form.

In nerves it may be demonstrated by Kuehne's experiment on the sartorius of the frog. The end of the muscle, after being slit longitudinally for a small distance, is stimulated at one tip, which causes contraction of both tips. Cross-conduction between muscle fibers being impossible, the impulse generated in the nerve fibers of one tip must pass back to other branches of the same nerve fiber, and thus excite the other tip. A similar experiment may be made on the electrical organ of *Malapterurus*. The anterior roots of spinal nerves which contain fibers transmitting normally in only one direction may be shown to transmit also in the opposite direction by means of the electrical change accompanying a nerve impulse.

The *rate* of conduction varies in different tissues, and is roughly related to the function. In muscles all gradations are to be found, from the 0.02 to 0.03 meter per second of the smooth muscle fibers of the rabbit's ureters to the 10 or 13 meters per second in human muscle. The rate in nerves may be put at 27 meters per second in frogs and 35 meters per second in man. The conduction process sweeps over irritable tissue in the form of a wave, which in muscle is about 300 mm. long, while in nerves it varies from 18 to 140 mm. in length. Conduction is influenced by the same factors that affect contractility.

Nature of Nerve Impulse.—The nature of the process has not been determined, but must be either of physical or chemical character. The balance of evidence, at present, seems to favor the view of its chemical character. It has been shown by van't Hoff that the velocity of chemical reactions is increased twofold or more for each rise of $10°$ or more in temperature. The temperature co-efficient, therefore, lies between 2 and 3. For most physical processes, on the other hand, the temperature co-efficient lies between 1 and 2. The temperature co-efficient for the velocity of a nerve impulse is equal to about 2, which indicates that the underlying process is chemical in nature. It is very suggestive that the conductivity of nerve depends upon an adequate supply of oxygen. When a nerve is surrounded by an oxygen-free atmosphere it slowly loses its conductivity, which, however, is promptly restored upon the admission of oxygen. Anesthetics, narcotics, and cold likewise suspend conductivity.

Just as in muscle functional activity is accompanied, sooner

or later, by the phenomena of fatigue, so it was hoped that continuous functional activity of nerve fibers might exhibit similar results. The obvious conclusion, then, would have been that the conduction of the nerve impulse is associated with a chemical change. Most of the effort expended in this direction has been negative in results except that it proves the practical unfatiguableness of nerve fibers under ordinary conditions of stimulation. Under special conditions, when the irritability of nerve fibers has been depressed by narcotics or by lack of oxygen the fatiguing effect of stimulation can be demonstrated. It shows itself by a lengthening of the refractory period following stimulation. Thus, when two stimuli follow each other at an interval of time less than 0.006 second, then the second stimulus is ineffective in arousing a nerve impulse. This is normally due to a short-lasting fatigue following the first stimulus. This period necessary for recovery is increased by functional activity of nerve fibers.

Further but not conclusive evidence for metabolism in nerve fibers has been furnished by Waller, who showed that the action current of a nerve is increased in intensity by a short period of functional activity, *i. e.*, stimulation with interrupted induced current, just as it is by passing over it for a brief interval a stream of carbon-dioxide gas. Many physiologists, therefore, conceive the nerve impulse as a wave of chemical change which, once started, is self-propagated along the fiber. The electrical change that accompanies it is considered as due to the formation of electrolytes in the reaction and the accumulation of negatively charged ions. Those who believe in the physical character of the nerve impulse base their conception upon the fact that no consumption of material can be demonstrated under ordinary conditions. It is assumed that an electrical charge constitutes the nerve impulse which passes over the nerve because it is essentially a "core conductor." Such a "core conductor" may be constructed out of a glass tube filled with 0.6 per cent. sodium chloride, and in the axis of which there is stretched a platinum wire. The neurofibrils are likened to the platinum wire; the perifibrillar substance to the sodium chloride solution. In such a model many of the electrical phenomena are similar to those shown by nerve.

Nerve Degeneration and Regeneration.—Whether physical or chemical in character, the propagation of a nerve impulse is dependent upon the living condition of the nerve fibers, and this in turn is dependent upon the maintenance of nutritive relations with the nerve cells. Every nerve fiber is the axis cylinder of a nerve cell. If it be cut away from the cell it will degenerate. In a mammal in about four days. A typical degeneration can only take place in living fibers. The fibers break up into ellipsoidal segments of myelin, each containing a piece of axis cylinder. The segments break up into smaller fragments and undergo absorption. Simultaneously the nuclei of the neurilemmal sheath have begun to multiply, and each has formed about itself a mass of protoplasm, so that finally a continuous band of protoplasm, known as an "embryonic fiber" or "band fiber," has been formed. If, at this time, the connection with the central stump of the nerve is established, the "embryonic fiber" becomes changed into a normal fiber, probably by a growth of the axis cylinder from the central stump. The latter, during the process of degeneration and regeneration, remains practically unaltered. A typical degeneration may extend back for several internodal segments. If, however, no functional union has been reëstablished the central cells undergo atrophy in the course of time. Usually distinct histological changes may be observed within the first twenty-four hours in that the chromatin material loses its staining power. The cell becomes swollen and the nucleus assumes an excentric position. These changes progress for eighteen days or so, after which the cell may regain its normal appearance.

Myogram.—The movements made by striated muscles are too quick to be followed accurately by the eye, so that resource is had to what is known as the *graphic method*. The muscle, by means of a mechanism, is made to write its contractions and relaxations on a surface moving at a uniform rate. The entire arrangement constitutes a *myograph*, and the record thus obtained is a *myogram*. The myogram of a simple muscle contraction consists of three distinct portions. Immediately succeeding the stimulation is an interval (*latent period*) of about $\frac{1}{100}$ of a second, during which the muscle makes no apparent change. During the next $\frac{4}{100}$ of a second the muscle shortens, and during the last $\frac{5}{100}$ of a second it lengthens again. Contraction

and relaxation take place at first slowly, then faster, and finally slowly again. The entire time involved may be put at an average of $\frac{1}{10}$ of a second. The time relations vary with the nature of the muscle and the conditions under which it works. Finer methods of determination have reduced the latent period to a mechanical and an electrical latent period of 0.004 and 0.001 second respectively. The latent period of the motor end plates is about 0.002 to 0.003 of a second. When the striated muscle of a frog is submitted to a series of equal induction shocks at a regular rate, a series of contractions are recorded, of which the first four or five may fall in height, and are known as the *introductory* contractions. After this there is an increase in the height regularly to a maximum which forms the *"treppe"* or *staircase*. Following this again the contractions lose in height until they disappear, which is known as fatigue.

The *staircase contractions* result from the fact that each stimulation occasions a heightened irritability, so that the succeeding stimuli become more effective. *Fatigue* is caused by the accumulation of waste products and to the consumption of available nutriment. When the rate of stimulation is increased, the separate muscular contractions may not come down to the base-line, giving rise to the phenomena of *contracture*. This condition may be explained by the fact that as the muscle contracts it becomes fatigued, resulting in a prolongation of the relaxation. A second stimulus reaches the muscle before the contraction resulting from the first is over. There is a summation of contractions. *Double contractures* are given by muscles composed of two distinct kinds of fibers, which react differently to the same stimulus (Fig. 11).

The *pale fibers* react quickly and are soon fatigued, while the *dark fibers* have greater endurance. The summation of contractions of the pale fibers occurs first and quickly raises the base line. As they become fatigued, the base line gradually sinks until the dark fibers in a similar manner raise it again. When both dark and pale fibers are fatigued, separate contractions, and relaxations no longer take place, and the base-line gradually sinks. With still more frequent rates of stimulation the staircase and contracture effects are merged into one another, giving rise to a very great height of contraction. As the curve

is wavy or unbroken, it is known as an incomplete or complete *tetanus*.

Tetanus is the result of three factors:

1. Increase of irritability.
2. Summation of contractions.
3. Support offered by contracture.

FIG. 11

Serial contractions of gastrocnemius of frog, showing double contracture, introductory contraction, staircase, and fatigue. Two stimuli per second, maximal induced current. Muscle weighted with 10 grams and used three days after pithing frog.
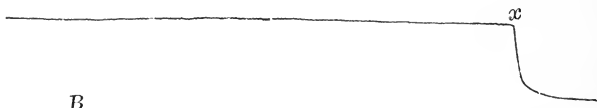
Final portion of curve *A*, showing gradual relaxation due to fatigue; *x*, cessation of stimulation.

All *normal physiological contractions* must be regarded as short tetani, and the normal impulse as a discontinuous form of excitation. As evidence of this may be cited the fact that muscles give out a sound when contracting, implying that their finest particles are in a state of vibration. Wollasten determined the rate to be from 36 to 40 per second. By means of vibrating reeds Helmholtz reduced the rate 18 to 20 per second, which gives a tone imperceptible to the ear. Lately the rate has been studied by a new and much more reliable method. Each separate stimulus to a muscle causes a distinct electrical variation. By means of a string galvanometer these electrical changes may be registered and their rate determined.

The latter varies for different muscles as follows: M. deltoideus, 58 to 62; M. gastrocnemius, 42 to 44; M. masseter, 88 to 100, etc. These figures represent the rate of discharge of nerve impulses per second by the nerve cells of the spinal and cranial motor nuclei.

The *energy* liberated by muscle appears in *mechanical, thermal,* and *electrical* form. The last is so small that in quantitative determinations it is negligible. Only one-fourth to one-twentieth of the chemical energy liberated by the muscle appears as mechanical energy. The work done by a muscle depends upon its nature and condition, the stimulus applied, and the mechanical conditions under which the work is done. *Work* is calculated by multiplying the load into the height to which it is lifted. The *absolute muscular force* of a muscle is the maximum weight that it can lift per unit cross-section. This for the frog is 3 kilograms per square centimeter. The heat liberated by active tissue is measured by a *thermopile* or a *bolometer.* The first consists of a certain number of junctions of two dissimilar metals like antimony and bismuth, which develop an electrical current whenever any two of the junctions are at a different temperature. The action of a bolometer depends upon the fact that the electrical resistance of a wire varies with the temperature. An isolated muscle has by means of these instruments been found to produce by a single contraction, per gram of muscle substance, sufficient heat to raise 3 milligrams of water 1 degree centigrade.

Electrical Phenomena of Nerve.—Electrical energy is exhibited by many forms of living matter. In order to study its manifestations in muscle and nerve it is necessary to take special precautions by using non-polarizable electrodes in place of the ordinary metal contacts. This for the following reason:

It is now assumed generally that the molecules of any solution which is a conductor of electricity are in a *state of dissociation—i. e.,* the molecules are divided into two or more parts, called *ions.* Thus sodium chloride in water becomes separated into a sodium ion charged positively with electricity and into a chlorine ion charged negatively. The passage of a galvanic current through such a solution is accomplished by means of the ions, and gives rise to electrolytic phenomena consisting of a migration of the positively charged ions or *kations* to the negative

pole of the galvanic circuit. In like manner the negatively charged ions or *anions* move toward the positive. This effect is brought about in any moist tissue that will conduct, and the tissue is then said to be *polarized*. The difference of potential between the kations and anions sets up a current (polarization current) in a direction opposite to that of the inducing current.

It happens thus that a polarization current produced in any tissue, like nerve, may completely disguise the weaker differences in electrical potential due to the tissue itself. Non-polarizable electrodes consist essentially of a metal in a solution of one of its own salts. The zinc-zinc sulphate combination has been found most nearly perfect. One form of this electrode consists of a glass tube, plugged at the end which is to come in contact with the tissue with a stiff putty of kaolin made up in physiological saline. Into the other end of the tube are inserted a saturated solution of zinc sulphate and a strip of amalgamated zinc. The liquid and metal portions of the circuit come into contact at the junction of the zinc and zinc sulphate. The dissociation which takes place at the kathode liberates a zinc kation which deposits itself upon the zinc electrode, while the sulphion at the anode unites with an atom of zinc to form zinc sulphate, which remains in solution. In this way polarization is largely prevented, and the tissue comes into contact only with the physiological saline in the kaolin plug.

Whenever any portion of a tissue becomes active, or in any manner undergoes katabolic changes, a difference of potential manifests itself in that the active portion becomes negative to the rest. The difference of potential is generally small, requring a sensitive galvanometer or electrometer to measure it, but in some electrical fishes becomes as high as 200 volts. When a muscle or nerve is intact and uninjured, it gives no evidence of differences of potential, and is therefore said to be *iso-electric;* but when the ends are cut, so as to present two sections at right angles to the longitudinal surface, it will be found upon testing with non-polarizable electrodes, and a suitable galvanometer, that the cut and therefore dying ends are negative to the uninjured longitudinal surface.

The current flows from the injured tissue through the muscle or nerve to the electrode on the longitudinal surface, thence

through the galvanometer back to the starting point. Points equidistant from the centre on the cross-section and from the equator on the longitudinal surface are at the same potential. A current obtained by mutilation of the tissue is known as a *current of injury*, of *rest*, or of *demarcation*. In a cat's nerve it has been found to equal 0.01 and in an ape's nerve 0.005 of a Daniell cell. *Dead tissue gives no current.*

It has been found than when living tissue is stimulated, the activity accompanied by katabolic changes sweeps over it in the form of a wave. As the latter, in muscle or nerve, passes by the electrodes it brings about differences of potential which are indicated by a galvanometer. These differences of potential give rise to *currents* of *action*. When a current of action is superimposed upon a *current* of *rest*, the needle of the galvanometer, having been deflected to a certain extent by the latter, is made to move back toward the zero point, giving rise to a *negative variation*. When the nerve of one (*A*) of two nerve-muscle preparations is laid lengthwise over the muscle of the other preparation (*B*), and the nerve of *B* is stimulated with an interrupted current, both muscles are thrown into tetanus. That this phenomenon is not due to a spread of the exciting current through the preparations is shown by ligating the nerve *B* between the electrodes and the muscle, when all contractions cease. As a matter of fact, the muscle fibers of *B* give rise to currents of action that are circuited through the fibers of nerve resting on its surface. The nerve fibers of *A* are thus stimulated and cause the muscle to contract. *This phenomenon is known as secondary tetanus.* As the wave of a nerve impulse sweeps by the electrodes, it changes the potential successively of one and then of the other, so that the needle of the galvanometer is deflected at one instant in a positive direction, and in the next in a negative direction. Currents of action are therefore *diphasic*. Changes of irritability due to the passage of a constant current have been alluded to under electrotonic changes. There are to be observed at the same time variations in the electrical currents of the nerve itself, *i. e.*, variations in the currents of rest. The constant current causes in the nerve outside of the electrodes the appearance of another current that has the same direction as itself, and is called the *electrotonic current*. The electrotonic current adds to or takes away from the cur-

rents of rest according as they are flowing in the same direction or in an opposite direction. The strength of the electrotonic current is dependent upon the strength of the polarizing current, the length of the region between the electrodes, and the condition of the nerve. A dead nerve does not manifest electrotonic currents, and they may be stopped by a ligature or by crushing the nerve.

Rigor Mortis.—Whenever a muscle dies, it undergoes a change manifesting itself in a loss of translucency, of extensibility, and elasticity, by the development of a gradual contraction, of increased heat production and acidity. This change is called *rigor mortis*. It usually affects the body in regular order, the jaw, neck, trunk, arms, and legs being influenced one after the other. In general, the more active the protoplasm the sooner does it pass into rigor. During life the central nervous system is continually sending impulses to the muscles, keeping them in a slight state of tension called *muscle tonus*. If the muscles are severed from the central nervous system by curare, the development of rigor is delayed. Cold delays and warmth (38° to 40° C.) favors rigor.

The chemical changes that take place during the onset of rigor may be briefly summarized as follows: There is a coagulation of protein material of the muscle plasma. Possibly under the influence of an enzyme, myosin and myogen are converted to the insoluble forms—myosin fibrin and myogen fibrin. The increased acidity is due, certainly, to the development of lactic acid and carbonic acid; perhaps also to other acid bodies. A change in the glycogen content by rigor has not been definitely established.

Rigor caloris is caused by the precipitation of various proteins of the muscle by heat.

Chemistry of Muscle and Nerve.—Muscle plasma, in addition to water, contains a great number of substances which are difficult to classify. They may be grouped, however, as follows: Proteins, carbohydrates and fats, nitrogenous waste products, lactic acid, phosphocarnic acid, pigments, ferments, and inorganic salts.

The most important substances isolated from the myelin of nerve fibers are lecithin, cholesterin, and cerebrosides. Lecithin ($C_{42}H_{84}NPO_9$) is a waxy, yellowish, hygroscopic

substance containing 4 per cent. phosphorus. When decomposed by the action of alkalies it yields glycerophosphoric acid, cholin $(C_5H_{15}NO_2)$, and fatty acids such as oleic, palmitic, and stearic. This decomposition occurs in the body when nerves undergo degeneration. Cholin has been found in the liquids of the body in the case of degenerative diseases of the nervous system. Cholesterin $(C_{27}H_{46}O)$ is widely distributed among the tissues of the body, and is found especially in the white matter of the nerves. Lecithin and cholesterin usually occur together, and it is a most interesting fact that cholesterin antagonizes lecithin in the activation of cobra venom. The cerebrosides contain nitrogen but no phosphorus. They are found in myelin in combination with lecithin. They belong to the group of glucosides, for on hydrolytic decomposition they give rise to the carbohydrate group, galactose.

QUESTIONS ON CHAPTER XI

What is a nerve-muscle preparation?
Define a stimulus. How many classes are there?
Upon what factors do the results of stimulation depend?
Why is an electrical stimulus usually a desirable one?
Distinguish between voltaic and induced currents.
Define opening and closing shocks. Which is the stronger?
Tell why the breaking induced current is stronger than the making.
What are subminimal and supermaximal stimuli?
What changes take place in the contraction of a muscle as the excitation increases in strength?
What is Du Bois-Reymond's law?
Illustrate how density of current affects its exciting power.
Discuss the results of duration of stimulus.
What are ascending and descending currents?
Discuss changes in irritability and conductivity of a nerve during electrotonus.
What are anelectrotonus and katelectrotonus?
What is the relation of rise of irritability to excitation?
Discuss in detail Pflüger's law.
At what points may an impulse be generated when a nerve *in situ* is subjected to a constant current?
In what order do the contractions occur as the strength of current is increased? Give reasons.
What is meant by the "reaction of degeneration?"
Upon what factors does the irritability of a preparation depend?
Discuss the effect of changes in environment upon the irritability of tissue.
Discuss the effect of severing a nerve fiber from its cell body.
How does functional activity alter irritability?
Distinguish between fatigue and exhaustion.
Give proof that waste products are formed during activity.

What distinguishes between an electrical current and a nerve impulse?
Give proof that conduction may pass in all directions in protoplasm.
Give rates of conduction in various tissues.
What factors affect conductivity?
What are the lengths of the conduction waves in muscle and nerve?
Discuss thoroughly the nature of a nerve impulse.
Describe a typical degeneration and regeneration of a nerve fiber.
By what method are muscle movements studied?
Describe a simple myogram.
What is the latent period of the motor end plates?
Discuss the introductory contractions, staircase contractions, and fatigue.
What is the cause of contracture?
What factors cause tetanus?
What is the nature of voluntary contractions?
Discuss the reasons for thinking voluntary contractions tetani.
How is the chemical energy of muscle liberated?
What proportion appears as mechanical energy?
Upon what factors does the work of a muscle depend?
How is work estimated?
What is absolute muscular force? Give its value in frog's muscle.
How is the heat liberated by tissue measured?
How is the electricity liberated by tissue measured?
When are muscles iso-electric?
What is a current of rest? Trace its path.
What are currents of action?
What causes a negative variation?
Explain secondary tetanus.
Explain why a current of action is diphasic.
Discuss electrotonic currents.
How does rigor mortis manifest itself?
In what order does it affect the various portions of the body?
What is the cause of rigor mortis?
What is the cause of rigor caloris?
What factors influence the onset of rigor?
Give the chemistry of muscle and nerve.

CHAPTER XII

CENTRAL NERVOUS SYSTEM

THE entire nervous system, for the sake of convenience, is divided into a number of parts:

1. *The central nervous system* or the cerebrospinal axis (brain and spinal cord).

2. *The peripheral nervous system* (spinal and cranial nerves and ganglia, sympathetic ganglia and nerves). Physiologically considered, such a division of the nervous system has no particular significance; the functions of these parts are intimately related and dependent upon one another, and form such an indivisible unit that any detached group of nervous structures would have no meaning. The essential constituents of the nervous system are separate but contiguous nerve cells or neurons. A *neuron* is meant to include every part of a nerve cell under the control of a given nucleus. It consists of the cell body and all its outgrowths. Of the latter, the *axons* are of various lengths, some in man spanning almost the entire length of the body. The ends of the axons and of the branches which an axon gives off along its length are divided into fine twigs or *terminal arborizations*. The remaining branches of the nerve cell do not attain the length of the axon, but very soon divide dichotomously, and they also form, finally, finely divided terminal arborizations. The arrangement of neurons is such that the end brush of the axon of one cell is in intimate relation to the end brush of the dendrite of another cell. Therefore, an impulse generated in any one neuron is transmitted to its neighbor, which in turn passes it on to the next neuron.

It is the function of the central nervous system to bring the body into relation with changes in its environment and to preserve the harmonious working of all its organs. Widely separated parts of an organism, therefore, are bound together by

nerve structures. Nerves do pass out indiscriminately, but are grouped together into anatomical structures forming the cranial, spinal, and sympathetic systems. An intelligent appreciation of the physiology of the central nervous system must rest upon a knowledge of its structure. This, however, is excessively intricate and but incompletely known. In its simplest aspect it may be regarded as based upon reflex arcs, made up of afferent and efferent neurons. These with perhaps one or more central cells or tract cells form a chain of nerve cells which conveys a disturbance arising in a peripheral sensory end organ to the central nervous system and back to a reacting organ (muscle or gland). This event, if it is involuntary, is a *reflex act*.

Reflexes.—Reflexes fall into three groups: (1) Simple reflexes, in which a single muscle is effected, for example, the winking reflex: (2) coördinated reflexes, in which a number of muscles react in time and extent so as to produce an orderly and useful movement; (3) convulsive reflexes, in which many muscles contract simultaneously, producing disorderly and useless movements. The latter may be produced by a very intense stimulation or by heightening the irritability of the central nervous system, as, for instance, by the injection of strychnine or tetanus toxin. The mechanism underlying a simple reflex may be conceived to be that of a simple reflex arc, consisting of a receiving structure or *receptor*, a conducting structure or *conductor*, and a reacting structure or *effector*. The greater complexity of the coördinated reflex implies a corresponding complexity of reflex arc, so that an impulse reaching the cord along a single afferent fiber has presented to it the choice of many potential routes. The precise route or routes followed depends upon the varying resistances offered by the synapses. A nerve impulse comes into the cord along a path traversed only by itself and others of like kind, but passes to the effector organ along a path used by many different impulses coming from widely separated areas of the body. The latter is, therefore, designated as the *final common path*. If two impulses, destined when acting alone, to produce antagonistic effects, should simultaneously enter upon the same final common path, then only one becomes effective.

FIG. 12
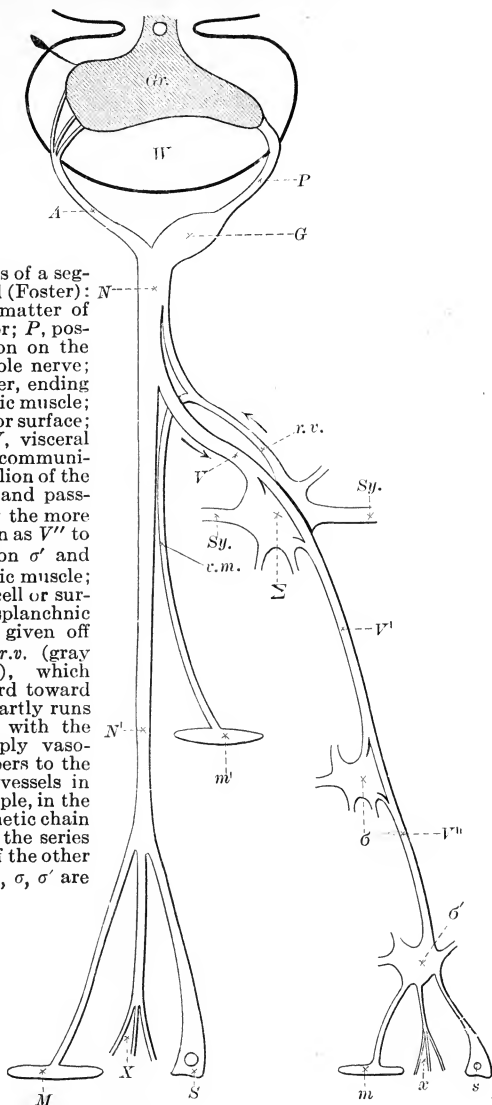
Scheme of the nerves of a segment of the spinal cord (Foster): *Gr.*, gray; *W*, white matter of spinal cord; *A*, anterior; *P*, posterior root; *G*, ganglion on the posterior root; *N*, whole nerve; *N'*, spinal nerve proper, ending in *M*, skeletal or somatic muscle; *S* somatic sensory cell or surface; *X*, in other ways; *V*, visceral nerve (white ramus communicans) passing to a ganglion of the sympathetic chain Σ, and passing on as *V'* to supply the more distant ganglion σ, then as *V''* to the peripheral ganglion σ' and ending in *m*, splanchnic muscle; *s*, splanchnic sensory cell or surface; *x*, other possible splanchnic endings. From Σ is given off the revehent nerve *r.v.* (gray ramus communicans), which partly passes backward toward the spinal cord, and partly runs as *v.m.* in connection with the spinal nerve, to supply vasomotor (constrictor) fibers to the muscles (*m'*) of bloodvessels in certain parts, for example, in the limbs; *Sy*, the sympathetic chain uniting the ganglia of the series Σ. The terminations of the other nerves arising from Σ, σ, σ' are not shown.

Inhibition.—Inhibition is one of the most fundamental phenomena of spinal reflexes. If, in a frog, the cerebral hemispheres are removed, stimulation of the exposed cut surface with crystals of sodium chloride will greatly depress or entirely inhibit the ordinary reflexes following stimulation of the skin. Removal of the stimulating substance from the cut surface by washing with physiological saline restores the reflex activities of the cord. An example of an inhibition of a reflex is afforded by the well-known device of preventing an act of sneezing by pressing upon the upper lip. A change of conditions in the spinal cord may permit excitation of a given group of muscles by the stimulation of an afferent path which is usually inhibitory for them. For instance, stimulation of the internal saphenous nerve in a decerebrate dog always produces inhibition of the quadriceps extensor involved in the knee-jerk. Poisoning with strychnine so alters the cord that stimulation of the nerve now produces reflex contraction instead of relaxation. The importance of inhibition in normal movements of the body is strikingly shown by the phenomenon of *reciprocal innervation.* By this is meant the simultaneous relaxation or loss of tone of an extensor muscle when the antagonistic flexor is stimulated reflexly.

Spread of Impulses in Spinal Cord.—As the strength of the stimulus used in evoking a reflex movement is increased, the effect becomes more and more extensive, spreading out or irradiating in various directions. For purposes of description of reflex action the sensory surface of the skin is divided into a number of areas related to definite portions of the cord, on the one hand, and to definite muscles, on the other. Such areas are the cervical, the brachial, the thoracic, the crural, and the caudal. On this basis spinal reflexes are classed as long or short. The short reflexes are those in which the muscular response takes place in the same region as the application of the stimulus. Long reflexes, on the other hand, involve the musculature of one region when the stimulus is applied to the receptive area of another region. For short reflexes a number of rules have been determined which may be stated as follows: (1) It is easier to excite reflex contractions involving a given efferent nerve, upon stimulation of a given afferent nerve, the closer their spinal segments lie together; (2) for each afferent nerve

there exists in its own special segment a reflex motor path of highest sensitiveness and effectiveness; (3) the various motor mechanisms in the same spinal segment are of unequal accessibility over local afferent channels; (4) groups of motor cells simultaneously discharged by reflex action enervate synergic muscles (those which act in the same direction in effecting movement), and not antergic muscles (those which antagonize each other).

For long spinal reflexes it may be stated that irradiation takes place more easily down than up the cord. It is easier for irradiation to cross the cord than to pass up the cord, but not as easy as it is to pass down the cord.

In the combining of reflexes it is possible to distinguish between simultaneous combination and successive combination. The movements are orderly and are harmonious because the spread of the reflexes follows a definite sequence, determined partly by the varying resistance of the synapses, and partly by the anatomical relations of afferent and efferent paths. The final common path, furthermore, while open to the afferent arcs that elicit the movement, must be closed to other afferent arcs which might disturb the reflex. In addition, there is evidence that frequently the final common paths are more widely open to the arcs in question by a reënforcing or facilitating influence of distant arcs which are simultaneously excited. Finally, the final common paths to antagonistic muscles must be closed through inhibition.

Afferent Paths to Brain.—The afferent impulses that enter the cord along the posterior roots may pass to the brain along any of many paths:

1. They may pass directly up through the posterior median column. Their course will then be interrupted by synapses in the nucleus gracilis and the nucleus cuneatus. The path is then continued across the middle line by the arcuate fibers of the sensory decussation and thus along the fillet, through the hinder part of the posterior limb of the internal capsule to the cerebral cortex. This path may be interrupted by cells in the thalamus.

2. They may pass to the cells of Clarke's column. From thence they pass up the direct cerebellar tract and through the restiform body to terminate in the posterior and median

portions of the vermiform lobe. The superficial gray matter of the vermis is connected by association fibers with the dentate nucleus, and the dentate nucleus by the superior peduncle with the opposite cerebral hemisphere.

3. They may pass to the anterolateral ascending tract of the same side after passing through cells of origin in the spinal gray matter. They pass thus to the superior peduncle of the cerebellum, and enter the gray matter of the superior worm.

4. They may cross the middle line, after entering the cord, through axons or collaterals in the anterior or posterior commissures and pass up one of the ascending tracts.

5. They may pass from neuron to neuron in the gray matter, passing out at various levels on the same or opposite sides of the cord.

Efferent Paths from Brain.—As the result of impulses reaching the brain, efferent impulses may be aroused which may make their way through the cord as follows:

1. Through the direct or crossed pyramidal tracts.

2. From the frontal part of the cerebral cortex, through the anterior limb of the internal capsule to the gray matter of the pons, and thence by way of the middle peduncle to the cerebellum.

3. From the occipital and temporal cortex, in the posterior limb of the internal capsule, to the pontine gray matter, and thus through the middle peduncle to the cerebellum. From the cerebellum they may pass to the nucleus of Deiters, and thence along the anterolateral descending tract to the anterior horn cells of the cord.

Paths of Motor and Cutaneous Impulses.—Lesions involving the pyramidal tract above the decussation of the pyramids cause paralysis of the opposite side of the body, but if situated below the decussation, a paralysis on the same side. The resulting paralysis, however, in many animals is only temporary. The motor area of the cortex may establish connections with the other side of the brain through commissural fibers, and in addition there are other corticospinal paths which can subserve volitional movements. On the other hand, hemisections of the cord in man and animals indicate that there is a sensory decussation. This for pain and temperature takes place chiefly in the cord. The paths for touch and muscular sense probably

cross mainly in the sensory decussation of the medulla. There exists a great deal of uncertainty as to the exact paths followed by the different cutaneous sensations. In syringomyelia, a condition in which cavities are formed in the gray matter, a frequent symptom is the loss in certain regions of sensibility to pain and to changes of temperature, while tactile sensibility is unaffected. In locomotor ataxia, in which there is an incoordination of movement, a degeneration in the posterior columns of the cord is an almost constant lesion. Afferent impulses from muscles and tendons resulting in tactile sensations and others serving as the basis of muscular sense, pass along these columns. The tracts of Gowers and Flechsig also probably carry impulses from muscles and tendons. The short endogenous fibers of the anterolateral column constitute a path in man for pain and temperature impressions—a path which is mainly or entirely a crossed one. The posterior columns have nothing to do with the conduction of painful impressions. Division of them causes hyperesthesia rather than anesthesia. If left intact, while the rest of the cord is cut, the animal is insensitive to pain below the level of the lesion.

Effects of Removal of the Spinal Cord.—It is necessary to perform this operation in several successive steps. The cord is first sectioned in the upper thoracic region, and then at successive times the lower thoracic, lumbar, and sacral region are removed. Very great care is required in the treatment of animals, but some have lived for long periods, during which the digestive, circulatory, and excretory organs performed their functions normally. The muscles of the hind limbs and trunk underwent complete atrophy. The bloodvessels, paralyzed at first, gradually recovered their tone. Taken all together, the animal showed a decided lack of adaptability. Its power of preserving a constant temperature was more limited than normal, and the susceptibility to inflammatory disturbances in the visceral organs was greatly increased.

Tonic Activity of the Cord.—In performing Brondgeest's experiment, a frog whose brain has been destroyed is suspended so that the legs hang down. Then one sciatic nerve is cut. As a result the leg on the corresponding side hangs a little straighter than the other. This is due to the fact that the feeble impulses which the cord is continually discharging

along motor nerves are cut off. These impulses are, perhaps, largely reflex in nature, for removal of the skin of the leg, or section of the posterior roots, leaving the anterior roots intact, produces the same result. There is abundant evidence that in the case of many special centres of the brain and cord, such a tonic activity exists. The degeneration of muscles after section of their motor nerves favors the idea that a tonic activity of the cord favors their nutrition, since there is no evidence for the existence of special trophic fibers. The rigidity of the muscles, often observed in paralysis from lesions of the central nervous system, is also, at least partly, due to reflex impulses. In such cases myotatic irritability is increased; the knee-jerk and the ankle clonus, etc., are exaggerated. Myotatic irritability depends upon a reflex muscular tone.

Knee-jerk.—If the leg is placed in an easy position, as when it rests on the other leg, and a sharp blow is directed against the patellar tendon, the foot will be brought forward with a sudden jerk. This is known as the knee-jerk, and is caused by the sudden contraction of the quadriceps femoris. Physiologists are divided in the explanation of this phenomenon, some regarding it as a true reflex, while others maintain that the contraction of the muscle is due to a direct stimulation of the muscle by vibrations set up in the tense tendon.

Considered as a reflex, the afferent path of the impulses is over fibers starting in the patellar tendon, running in the anterior crural nerve, and reaching the cord by the posterior root of the fourth lumbar nerve in man. The centre for the knee-jerk lies in the third and fourth lumbar segments of the cord. The efferent path is over fibers in the anterior crural nerve which leave the cord by way of the anterior roots of the third and fourth lumbar nerves. If any portion of this reflex arc is destroyed, the knee-jerk is no longer to be obtained. It may be augmented or depressed by nervous impulses from many parts of the central nervous system. It is reënforced by cutting the nerves of the antagonistic muscles, and depressed by stimulating the central ends of these nerves. This is explained by the fact that flexor muscles send impulses to the spinal centre, and according to their condition influence the contractions of the extensors.

It is found that a deficiency of the knee-jerk exists usually,

but not always, with a subnormal tension of the tendon, while a hypertonic state gives rise to an exaggerated jerk.

When the nerves of the ligamentum patellæ have been divided the knee-jerk is obtained in undiminished strength; nevertheless, some sort of reflex is involved, for division of the posterior roots that enter into the anterior crural nerve abolishes it. According to some authors it depends upon mechanical stimulation of the highly stretched muscle by the pull of the tendon when struck. It has been claimed that the time involved, 0.03 of a second, is characteristic of a simple muscle twitch, but too short for a reflex, the briefest of which requires more than one-fourth again as much time. However, it is admitted that the tendon tap may cause an undoubted reflex knee-jerk on the opposite side, the interval between the tap and the contraction being about one-eighth of a second.

The variations found in the tendon reflexes are very considerable. In some perfectly healthy individuals no knee-jerk at all can be obtained. Local fatigue of the extensor muscles diminishes it, while general fatigue at first increases but later diminishes it too. Shutting off the blood supply will cause the knee-jerk to disappear in a quarter of an hour. Stimuli applied to the skin, or a clinching of the fists, increase it if applied not more than 0.2 to 0.6 second before the tendon is struck. This phenomenon is termed reënforcement. If applied sooner they cause an inhibition which reaches its maximum at an interval of from 0.6 to 0.9 second before the kick. Sound always reënforces the jerk, while light causes very little if any inhibition. Inhalation of anesthetics (chloroform, ether) extinguishes the reflex. It has been found in man that the knee-jerk was present immediately after decapitation, but usually injury to the cord permanently abolishes it. Lombard has shown that all the ordinary events of daily life are portrayed faithfully in changes in the knee-jerk. In deep sleep the knee-jerk is absent, but sensory stimuli too feeble to awaken the sleeper are manifested in an exaggeration of the tendon reflexes. An increased knee-jerk is a symptom of some spinal diseases. After removal of the right half of the cerebellum the knee-jerk on the homonymous side is more vigorous. A similar result follows section of the cerebellar peduncles.

Time Involved in Nervous Processes.—Whenever a nerve impulse passes from one neuron to another, there is a delay in its transmission. In the frog, for example, it takes twice as long for an impulse to pass from the middle of the cerebral hemispheres to the optic lobes as from the bulb to the lumbar enlargement, although the distance is much less. If one eyelid be stimulated electrically, both lids wink. The total time required for this reflex is from 0.066 to 0.057 second. Deducting the time required for the impulse to pass to and from the brain along the fifth and seventh nerves, and also the latent period of the orbicularis muscle, there remains 0.05 to 0.04 second for the time required in the brain. This time value may be regarded as an *average* of *simple reflex actions*. The individual values vary greatly. In general the time is shorter the stronger the stimulus. It is shorter when the reflex is confined to one side of the body than in cases where the impulse crosses to the other side, even if allowance is made for the difference in the length of the nervous path. The time depends, of course, on the condition of the cord, becoming greater during exhaustion and disease. The time becomes longer the greater the number of neurons involved. When the afferent impulse arouses sensation and consciousness, and the ensuing response is the result of a volitional effort, then the neurons involved are indefinite in number. The action is now a *reaction,* and the time is known as the *reaction time.* This time is shorter when the right hand makes a response to a stimulus to the left than when the response is to either auditory or visual sensations. But the shortest reaction time follows a visual excitation produced by direct electrical stimulation of the retina. Roughly, reaction times for cutaneous sensations are one-seventh of a second; for auditory sensations, one-sixth of a second; for visual sensations, one-fifth of a second.

A reaction period consists of three stages, corresponding to the times required by the impulse on its afferent path, its efferent path, and in the central nervous system. All three stages may vary independently. The time involved in the central stage is known as the *reduced reaction time.* It varies in different persons, and is known as the *personal equation.* When the subject is required to react to one of two or more possible signals, the reaction time may be prolonged from 0.016 to 0.062

second, the time varying with the sensation employed. It is shortened by practice, so that in time it becomes more of the reflex type.

Medical Significance of Reflexes.—Reflexes are separable into superficial and deep reflexes. The former are those which are aroused by stimulation of the surface of the body, *i. e.*, from *exteroceptive fields*. The latter are aroused from receptors in the depth of the organism, *i. e.*, from *proprioceptive fields*. Examples of superficial reflexes are the plantar reflex (drawing up of the foot when the sole is tickled), the cremasteric reflex (retraction of the testicle when the skin on the inside of the thigh is stroked), and the gluteal, abdominal, epigastric, and interscapular reflexes (contraction of the muscles in those regions when the skin overlying them is tickled). The reflex behavior of the great toe is of diagnostic importance. Normally, on tickling the sole, the toes are flexed toward the planta, but when a lesion of the pyramidal tract exists, as in hemiplegia, there is a dorsal flexion and the toe moves more slowly than normally. This is known as *Babinski's sign*. In children it is positive during the first few months of life.

An example of a deep reflex is the knee-jerk. Its absence is of the utmost importance in the detection of tabes dorsalis. When its presence is doubtful, it is necessary to use the reënforcing effect of simultaneously clasping the hands tightly. While in locomotor ataxia the posterior limb of the reflex arc is deficient, in anterior poliomyelitis the central and efferent portions of the arc are missing. In primary spastic paraplegia, associated with degenerative changes in the lateral columns, the deep reflexes are all exaggerated.

Cranial Nerves.—The cranial nerves, with the exception of the olfactory and optic nerves, arise from gray matter of the medulla and midbrain. The floor of the fourth ventricle is distinguished particularly by the abundance of nuclei from which the cranial nerves arise.

I. The *olfactory nerve* forms the pathway for the impulses giving rise to smell. The fibers pass from the sense endings of the nose to the olfactory bulb on the same side, and then by way of the olfactory tract to the gyrus fornicatus or to the temporal end of the gyrus hippocampi.

II. The *optic nerve* conducts impulses from the retina to the pulvinar, the corpora quadrigemina, and the external geniculate bodies. In man the fibers for the greater part cross in the chiasma. From the primary centers they are continued to the occipital cortex of the same side, passing through the occipital end of the internal capsule. The location of the centres is probably in the cuneus and surrounding parts. The calcarine fissure has been indicated by some as the most important ending.

III. The *motor oculi* is a purely motor nerve. Section paralyzes the elevator of the upper eyelid, giving rise to *ptosis;* paralysis of the muscles of the eyeball results in inability to move the eye up, down, or inward, while the unopposed action of the external rectus produces external strabismus; paralysis of the muscle of the iris causes the pupil to remain dilated, so that it does not respond to light; paralysis of the ciliary muscle prevents accommodation. The control of the pupil through a strong voluntary effort exerted through the third nerve shows itself in a contraction, when the eyeball is turned strongly upward and inward.

IV. The *patheticus* supplies the superior oblique muscle. Its section results in double vision, and the image seen by the affected eye appears obliquely and below that of the other eye. This may be corrected by inclining the head to the opposite side.

V. The *trigeminus nerve* breaks up into three branches; of these, the first and second are entirely sensory, while the third is motor. Section of the motor root of the nerve results in a paralysis of the muscles of mastication. Destruction of the sensory root results in complete anesthesia of the skin of the face and the mucous membrane of the mouth. The anesthesia of the conjunctiva, of the nostrils, and of the lips prevents the reflex self-protection which belongs to the parts, and they become easily injured. The nerve cells are located in the Gasserian ganglion. The peripheral axons extend to the skin, while the central axons upon reaching the bulb divide into a shorter branch, which extends cephalad, and a longer branch, which extends caudad, both connecting with cells in the substantia gelatinosa. One set of neurons is thought to pass direct to the cerebellum.

VI. The *abducens* supplies the external rectus muscle of the eye.

VII. The *facial* is a motor nerve which parallels in its distribution the sensory portion of the fifth. It supplies the superficial muscles which give the features the power of reflecting the emotions. If the nerve is sectioned, the face on that side is devoid of motion and becomes smooth and expressionless. The eyelids do not close and the lips do not oppose properly on account of the defective action of the orbicularis muscle. There is difficulty in drinking and in speaking for the same reason.

VIII. The *cochlear portion* of the auditory is the nerve of hearing. The cell bodies of these fibers are situated in the spiral ganglion of the cochlea, which is homologous with the dorsal root ganglia of spinal nerves. One axon reaches the organ of Corti, and the other passes to the bulb, where it terminates in the dorsal or ventral nucleus of the eighth nerve. The fibers entering the ventral nucleus may be continued to the superior quadrigemina, passing by way of the trapezium, the superior olive, the lateral lemniscus, and the inferior collicus. They may give collaterals to each, or may end in any of these gray masses. Cells of the dorsal nucleus send their axons across the floor of the fourth ventricle, forming the striæ acusticæ.

The *vestibular portion* of the eighth nerve transmits impulses from the ampullæ of the semicircular canals, and therefore serves the sense of equilibrium. The cell bodies of these fibers are located in the vestibular ganglion, and their central axons are divided into a branch passing cephalad and one passing caudad, which terminate with various nuclei, and also pass to the cerebellum.

IX. The *glossopharyngeal* nerve is the nerve of taste and of deglutition. It is motor as well as sensory in function. Its distribution is to all the muscles of deglutition, and stimulation contracts, while section paralyzes them. The very numerous connections of the nerve complicate its origin and interfere with a clear comprehension of the unaided function of the nerve. The cells of the fibers lie in the bulb on the medial side of the tractus solitarius. Their axons are sent cephalad through the medial lemniscus. Latest investigations have shown that the chief path of the taste sense is over the chorda tympani nerve,

which leaves the glossopharyngeal mainly a nerve of motor function.

X. The *afferent fibers* of the *vagus* convey impulses from the pharynx, esophagus, stomach, liver, pancreas, spleen, larynx, bronchi, and lungs. Their termination is near the *nœud vital*. The functions of the pneumogastrics are very numerous indeed. It is involved in respiration, deglutition, in the movements of the stomach, in the action of the heart, lungs, and viscera.

XI. The *spinal accessory* is a motor nerve. It arises by roots from the medulla and from the spinal cord. It supplies the trapezius and sternomastoid muscles so that after section forced respiration is impaired.

XII. The *hypoglossal* is a motor nerve. This nerve is important in mastication. In animals its section is followed by inability to drink on account of difficulty in lapping. In man section of the nerve prevents articulation.

The Medulla Oblongata.—In this portion of the brain are situated a great variety of so-called centres. This term implies that any particular physiological action can normally go on only as long as the area of location of the centre in question is intact. The more important of these centres are those which control the circulatory and respiratory organs. If the medulla is severed from the portion of the brain lying anterior to it the animal continues to live for a considerable period. Respiration goes on rhythmically and the bloodvessels retain their tone so as to maintain a normal blood pressure. On the contrary, destruction of the medulla, or of those areas only in which the respiratory and circulatory centres lie, is followed by a cessation of respiration and a loss of tone in the arteries which result in a rapid death.

The Cerebellum.—An authoritative statement of the functions of this organ is not possible. Flourens advanced the general idea that it serves as a central organ for coördination of voluntary movements, particularly the more complex movements necessary in equilibrium and locomotion. Luciani regards it as "an organ which by processes that do not awaken consciousness exerts a continual strengthening (reënforcing) action upon the activity of all other nerve centres." Sherrington "conceives of the cerebellum as the head ganglion of the proprioceptive system." Lewandowsky has suggested that "normally in

man the finer, more conscious movements of the body are controlled directly from the cerebrum, while the subconscious or dimly conscious movements of locomotion and equilibrium are regulated through the cerebellar centres.''

The first effect of removal of the cerebellum in a dog is a rigidity and tonic spasm of certain muscles. Later all the muscles of the body, especially those of the hind limbs and those which fix the head, lose their tone and contract with a peculiar want of steadiness. When one lateral half of the cerebellum is removed the muscles on the same side only are affected. In man extensive lesions of the cerebellum are accompanied by a marked inability to maintain an upright position, by giddiness, nystagmus, and tremor on attempting voluntary movements. In the ataxic condition from tabetic lesions the effect upon movements is increased by covering up the eyes (*Romberg's symptom*), the individual being then deprived of his visual stimuli as well as those coming by way of the muscular and cutaneous nerves. In cerebellar ataxia, however, the effect is not increased by the closure of the eyes, since the individual still possesses his paths of muscular and cutaneous sensibility. Cerebellar lesions give no sensory or voluntary paralysis, nor is there any psychical disturbance.

A striking symptom of cerebellar lesions are the so-called *forced movements*. They are not absolutely diagnostic, however, since they follow many unilateral injuries of the brain, *e. g.*, to the pons, crus cerebri, posterior corpora quadrigemina, corpus striatum, and cerebral cortex. These movements are movements toward the side of the lesion apparently beyond voluntary control. They are precisely like those following injuries to the semicircular canals. They may consist of a rotation around a longitudinal axis, or the animal may run around and around in a circle (circus movements); or, with the tip of its tail as a centre and its body as a radius, it may describe a circle; or, it may rush forward, turning innumerable somersaults. In man, forced movements associated with vertigo have been observed in tumor of the middle peduncles.

The connections of the cerebellum with other portions of the central nervous system are significant in considering its functions. These connections may be grouped under three heads:

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1. *Connections with the Cord.*—The cerebellospinal tract passes from the cord, through the restiform body, to the cerebellum, carrying impulses derived from terminations in muscles and tendons. It is still an undecided point whether impulses from the posterior columns may pass from the nuclei gracilis and cuneatus to the cerebellum. Ascending fibers arising in the reticular formation of the medulla and olivary nucleus pass to the cerebellum by way of the inferior peduncles, and probably, on the other hand, make connections with the sensory tracts of the cord or sensory nuclei of the medulla. Gowers' tract or the fasciculus anterolateralis superficialis also passes to the cerebellum *via* the superior peduncle; like Flechsig's tract, carrying impulses of deep sensibility.

2. *Connections with the Vestibular Nerve.*—This nerve arises in the semicircular canals, utriculus, and sacculus, and ends in the pons in several nuclei (Deiters', Bechterew's) and in the nuclei fastigii of the cerebellum. From Deiters' nucleus the vestibulospinal tract arises, passes to the cord, where it makes connections with motor neurons. Bechterew's nucleus gives rise to fibers which, passing with the medial longitudinal bundle, make connections with the motor nuclei of cranial nerves. The sensory nuclei of the vagus, trigeminal, and auditory nerves, and. primary end stations of the optic nerves, are said to send afferent paths to the cerebellum.

3. *Connections with the Cerebral Cortex.*—Fibers arising in the motor area of the cerebrum or anterior to this descend in the internal capsule and cerebral peduncles to the gray matter in the pons. A second set of neurons continues the path across the midline, and passing by way of the middle peduncles reaches the cerebellar cortex. A second connection with the cerebrum is made by fibers from the dentate nucleus, which, passing *via* the brachium conjunctivum, reaches the red nucleus and the thalamus. The latter are continued to the cerebrum. From the red nucleus, on the other hand, impulses may pass *via* the rubrospinal tract to motor centres in the cord.

The Cerebrum.—One of the recognized methods for the study of the functions of the central nervous system is that of extirpating definite portions and noting the effects. The cerebrum in many classes of animals has been dealt with in this way. In the frog, complete removal of the cerebral hemispheres

shows very little permanent effect. When shock has passed off, the animal draws up its legs, erects its head, and assumes the characteristic resting position of a normal frog. When placed on its back it quickly resumes the normal posture. If thrown into water it swims to a solid support and crawls out. Every time its flanks are stroked it will croak with almost fatal regularity. It jumps when stimulated and avoids obstacles placed in its way, showing that its visual reflexes are intact. It is said that more complicated reactions, depending upon the memory of past experiences, or the instincts, are absent or imperfect.

Removal of the cerebrum in pigeons throws the nervous, active animal into a stupid, lethargic condition. It sits in a drowsy attitude with its head drawn in, eyes closed, and feathers slightly erected. The animal maintains a perfect equilibrium upon a perch, and flies well when thrown into the air. With care and feeding it remains alive indefinitely. If allowed to starve it becomes restless from the effects of hunger, pecks aimlessly at the ground, not being able to actually seize a separate grain and swallow it. The reactions of the animal are more direct and predictable. When placed on a hot plate, it will, for a time, lift one foot after the other, and finally squat, but not fly. When dozing, a loud noise awakens it, but it exhibits no sign of fear.

In dogs the removal of the cerebrum is more difficult, and if performed at one operation leads to a rapid death. Goltz's dog, in which the brain was washed away in several successive stages, with a stream of saline, lived for a year and a half, when it was killed. The postmortem examination showed that all of the cortex had been removed except a small portion of the temporal lobe, which, being without connection with the rest of the brain, was functionless. A large portion of the corpora striata, thalami, and some of the midbrain had been removed. After the immediate paralysis had disappeared the animal moved easily, and showed a tendency to keep moving. There was no permanent paralysis of voluntary movements. If a painful stimulus was applied to the flank, he would growl or bark, turn his head to the place stimulated, but would not bite. No caressing would arouse signs of pleasure, and no threatening signs of fear. His memory records for the most part had been

destroyed. When starved he would show signs of hunger, and learned to feed himself when his nose was placed in contact with the food. He would reject food of disagreeable taste. When sleeping he gave no signs of dreaming.

The loss of the cerebral hemispheres would, no doubt, to a monkey be a heavier and more irremediable blow than to a dog. No one has succeeded in keeping a monkey alive after complete removal of even one hemisphere. In man, the gradual destruction of considerable masses of brain substance is not necessarily fatal. The result depends largely upon the situation of the lesion, for the cerebral cortex is not homogeneous in function. This is expressed by the term *localization of function.*

The Motor Area.—Definite experimental proof of cerebral localization was furnished by Fritsch and Hitzig in 1870, who showed that stimulation of the cortex in dogs in the region of the crucial sulcus gave definite movements. An enormous amount of experimentation has made it probable that the motor area in man lies along the anterior central convolution, and extends for only a small distance on to the mesial surface of the cerebrum (Fig. 13). It dips down to the bottom of the central sulcus, but does not extend behind it. Anteriorly it shades off gradually into inexcitable cortex. Within this area are localized movements of the head, face, mouth, tongue, ear, nostril, and vocal cords; movements of the neck, chest, abdomen, arm, and leg. Within each area smaller centres may be located by careful stimulation; thus, the arm and hand area may be subdivided into regions for the wrist, fingers, and thumb. The distribution of the areas follows in a general way the order of the cranial and spinal nerves.

The motor area, thus outlined physiologically, is the region from which the pyramidal system of fibers arises, and lesions in this part of the cortex are accompanied by paralysis of the muscles of the other side of the body, particularly of the limbs. The path taken by motor impulses is through the following structures: Corona radiata, internal capsule, cerebral peduncle, pons, anterior pyramids, pyramidal decussation, direct and crossed pyramidal tracts of the cord. In the pons some of the fibers cross the midline to end in the motor nuclei of the third, fourth, fifth, sixth, and seventh cranial nerves. Clinically, it is important to recognize the difference between the effects of

injury to the spinal and pyramidal neurons. Lesions of the anterior horn cells causes complete paralysis of the corresponding muscles, so that in time atrophy results. When the pyramidal neurons are affected, as in hemiplegia from unilateral lesions of the motor cortex, there is paralysis as regards voluntary control, but the spinal neurons being intact the muscles are open to reflex stimulation, which, being uncontrolled, owing
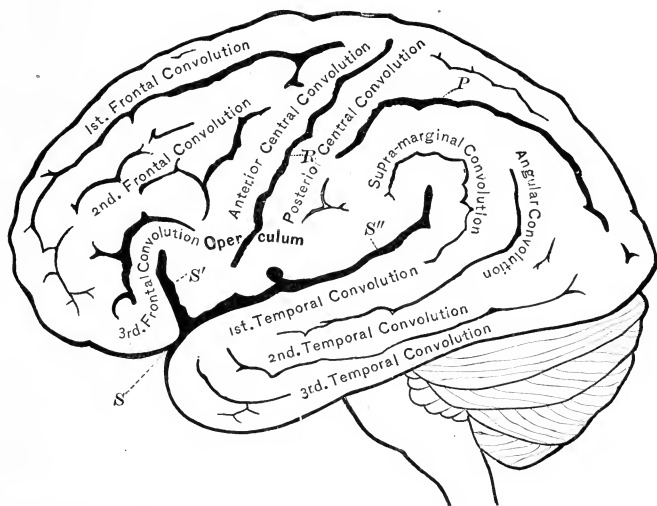
Plan of the human brain in profile (Dalton), showing its fissures and convolutions: *S*, fissure of Sylvius; *S'*, anterior branch; *S''*, posterior branch; *R*, fissure of Rolando; *P*, parietal fissure.

to lack of inhibition from the cortex, may lead to spastic rigidity. This condition, however, may be due in other cases to impulses coming by way of the rubrospinal tract. It is very suggestive, in this connection, that stimulation of the cortex leads to inhibition of tone, and to inhibition of active contraction, as well as to active muscular contraction. When, for example, in a monkey the part of the arm area which presides over extension of the elbow is stimulated, the biceps relaxes while the triceps

contracts. Related to this phenomenon is one known as *decerebrate rigidity*. It is a condition of prolonged spasm of certain groups of skeletal muscles which follows transection anywhere in the midbrain or in the posterior part of the thalamus. If the afferent nerves belonging to one of the rigid limbs are severed, it relaxes while the other limbs remain rigid. The spasm, therefore, is a reflex through nerves that supply joints, muscles, etc., and this reflex must be controlled by a centre situated somewhere between the cerebrum and the bulb, since section of the latter abolishes the rigidity. It is said that the centre is not in the cerebellum. The muscles involved in decerebrate rigidity are those, particularly, which are most easily inhibited from the cerebrum. Removal of the latter organ unmasks an action of a mechanism which tends to keep the muscles in tonic contraction.

Pathological paralyses are not always permanent, and it is an important question in what way recovery is brought about. Experimentally, extirpation of the hand area in monkeys renders the hand on the opposite side useless, but in a few weeks recovery has taken place to such an extent that it is freely but clumsily used. If, now, the corresponding area on the other side of the cortex is removed, a corresponding paralysis takes place, but the hand first paralyzed is not affected. On the contrary, it may be used more freely. In time recovery of hand number two takes place. If, then, the entire arm area of one side is extirpated, neither hand is affected, although paralysis of shoulder and elbow on the side opposite the lesion are obvious. The recovery of function of the hand, therefore, is not due to the acquisition of this duty by the hand area of the other side, nor does it seem to be due to the cortex immediately surrounding the hand area. According to some authorities it is due to a representation of the hand area in the postcentral gyrus acting through fibers that descend from that point to the optic thalamus, and thence through the rubrospinal tract.

Entire extirpation of the motor area of one cerebral hemisphere leads to extensive paralysis on the opposite side of the body, but it does not include all of the muscles, and, furthermore, it leads to some muscular weakness on the same side. Those muscles which ordinarily act in unison, like the diaphragm, intercostal muscles, and muscles of the larynx, are but little

affected. These muscles are bilaterally represented in the brain, so that they remain under voluntary control when the motor area of one side is destroyed. Mellus has shown that destruction of the centre of the great toe in monkeys is followed by a degeneration down both crossed pyramidal tracts. Whether the motor areas are only motor in function or include mechanisms serving sensation is difficult of determination. In two cases recently reported, where the anterior central convolution was stimulated in conscious patients, there was no sensation other than that arising from the change in position of the muscles thrown into contraction.

The Body-sense Area.—Lying posterior to the fissure of Rolando lies an area which is concerned with cutaneous and muscular sensations. There are cases on record in which lesions involving the anterior central convolutions were accompanied by paralysis on the other side without any detectable disturbance of sensibility, and, on the other hand, lesions of the posterior central and neighboring parietal convolutions have been described in which there was hemianesthesia without any paralysis. Lesion of the postcentral convolution, the supramarginal, the superior and possibly inferior parietal convolutions seem to involve chiefly muscular sense, pressure and temperature sense, and the judgments and perceptions based on these sensations, while the sense of pain is affected but little. Clinically the most positive and invariable symptom of lesions in this region is astereognosis, *i. e.*, a loss of the power to judge the form and consistency of external objects when handled. The area of the cortex concerned with the sense of pain has not been determined.

The paths followed by various cutaneous impulses as well as by those arising from muscles, tendons, etc., have already been traced in the cord. Some of these were found to lead to the nucleus gracilis, and to the nucleus cuneatus of the medulla. At this point a second set of sensory neurons arises, which for the most part runs ventrally as internal arcuate fibers, crosses the midline just in front of the pyramidal decussation, forming the sensory decussation. The path is then continued forward in the median fillet or lemniscus, and thus reaches the superior colliculus of the corpora quadrigemina and the thalamus. The important termination being in the ventral or lateral

nucleus of the thalamus. These neurons that end in the thalamus are continued by a third set of neurons which end in the parietal lobe of the cerebrum. In the medulla and pons the lemniscus receives accessions of sensory fibers from the sensory nuclei of the cranial nerves of the opposite side.

The Visual Area.—Removal of or injury inflicted upon the occipital lobes is followed by defects in vision. Goltz contended, from the reactions shown by his decerebrate dog, that some degree of vision remains after extirpation of the occipital lobes, for in this case the dog closed his eyes when a strong light was thrown into them. This, however, together with constriction of the pupil, may be regarded as a reflex through the midbrain, and not accompanied by a visual sensation. Complete removal of the occipital lobes is followed, apparently, by total blindness. When the lesion is unilateral the blindness affects symmetrical halves of the two eyes, a condition known as *hemiopia*. A right-handed destruction causes blindness of the two right halves of the retinæ, and, in accordance with the laws of projection of retinal stimuli, in the two left halves of the visual fields. There is, however, one very important exception. This is the fovea centralis, the area of most acute vision, which is not affected by unilateral lesions of the occipital lobes.

The paths over which visual impulses are carried to the brain undergo more or less decussation in the chiasma. This crossing is less complete in the mammalia than in the lower animals. In fish, reptiles, and birds the crossing is said to be complete. The fibers from the inner side of each retina cross, while those from the outer side do not decussate but pass into the optic tract of the same side. These fibers end mainly in the gray matter of the external geniculate body, but some pass to the pulvinar of the thalamus and some to the superior colliculus of the corpora quadrigemina. These structures are known as the *primary optic centres.* From these points the path is continued to the cortex through the occipitothalamic radiations lying in the posterior limb of the internal capsule. There are other fibers in connection with the optic nerves and tracts that must be mentioned. The inferior or Gudden's commissure consists of fibers passing from one optic tract to the other along the posterior border of the chiasma, connecting the internal geniculate and inferior colliculus of one side with those of the

other. It is believed to belong to the auditory path. There are fibers passing from the chiasma into the floor of the third ventricle which are thought to connect with the nuclei of the third nerve and to be concerned in the light reflex of the iris. Finally, there is supposed to be a superior commissure along the anterior margin of the chiasma connecting the two retinæ. The termination of the optic radiations is mainly in the cuneus, particularly along the calcarine fissure, and probably, in addition, in portions of the lingual lobe and on the external surface of the occipital lobe. Stimulation in these regions causes movements of the head and eyes.

The Auditory Area.—It is very probable that the auditory area lies in the superior temporal gyrus and in the transverse gyri extending into the fissure of Sylvius. Entire ablation of both temporal lobes is followed by complete deafness. Ablation on one side, however, is followed by impairment of hearing, so that it is probable that the fibers end partly on the same side and mainly on the opposite side of the cerebrum.

The fibers constituting the cochlear branch of the eighth cranial nerve arise from the cells in the spiral ganglion. These cells are bipolar. One axon passes to the cochlea, where the impulses aroused by sound waves are generated. The other axon passes to the pons. Here it may end in one of two nuclei, one lying ventral to the restiform body and known as the accessory nucleus; and one, dorsally, known as the tuberculum acusticum. The axons that arise from the accessory nucleus pass mainly to the opposite side by slightly different routes. Some go directly across toward the ventral side of the pons, forming the corpus trapezoideum; others pass dorsally around the restiform body, and then down through the tegmental region to join the corpus trapezoideum. The fibers of this cross band end in certain nuclei of gray matter on the opposite side of the pons, especially in the superior olivary body and in the trapezoidal nucleus, and then the path is continued forward by a third neuron. At the level of the superior olivary body the auditory fibers enter into the lateral fillet or lateral lemniscus. The secondary sensory fibers from the tuberculum acusticum pass dorsally and transversely, forming the band of fibers known as the auditory striæ, on the floor of the fourth ventricle. The fibers then dip inward at the *raphe*, and some of them cross

the midline to reach the lateral lemniscus of the opposite side with or without making connections with cells in the superior olive. Other fibers join the lateral lemniscus on the same side. In the lateral lemniscus the auditory fibers pass to the mid-brain and end in the gray matter of the inferior colliculus, the internal geniculate, and in the superior nucleus of the lemniscus. From this termination another set of fibers, the auditory radiation, continues forward through the inferior extremity of the internal capsule to end in the superior temporal gyrus. Stimulation of the cortex of the temporal lobe causes a pricking of the ears and turning of the head and eyes to the opposite side.

Smell and Taste Areas.—The evidence for the situation of these centres is scanty and dubious. In some cases of epilepsy in which subjective sensations of smell were present the uncinate gyrus was found diseased. The olfactory tract may be traced into this region. In animals of acute smell the uncinate gyrus is large. The centre of taste is supposed to be situated in the hippocampal convolution, posterior to the uncinate gyrus.

The Association Areas.—The motor and sensory areas of the cortex are surrounded by much larger areas known as association areas, in which the different sense impressions are synthesized into complex perceptions or concepts. These areas assume their myelin sheaths at a later period and are not furnished with projection fibers, as are the motor and sensory areas. They are, however, abundantly connected with the latter by tracts of association fibers. Knowledge is founded on sensations, aroused through the various sense organs which are combined in consciousness to form mental images. The sequence of phenomena in the external world is orderly, and, corresponding to this fact, the reflection of these phenomena in the sequence and combinations of sensations is also orderly. In the association areas memory records of past experiences are laid down in some unknown material change in the combinations of nerve cells and fibers. In these association or silent areas are included considerable portions of the occipital, parietal, and temporal lobes, nearly the whole of the island of Reil, and the greater part of the frontal lobe. Here, and particularly in the latter lobe, is the seat of intellectual processes. In the American crow-bar case, a tamping rod, as the result of a premature

blast, transfixed the left frontal lobe. The patient recovered and lived for nearly thirteen years, suffering no sensory or motor deficiency except occasional epileptic convulsions. His intellect was impaired; though previously a capable and decent workman, he became vacillating and inefficient in his work and profane in his language.

Aphasia.—One of the most fertile and suggestive fields in the study of associative mechanisms of the brain is to be found in the pathological condition of aphasia. In aphasia the power of intelligent communication by spoken or written language is lost. When this is due to an inability to interpret the meaning of the auditory and visual symbols by which ideas are conveyed, it is known as *sensory aphasia* or amnesia; when, on the other hand, it is due to an inability to clothe ideas in words, although the words may be present in the patient's consciousness, then the condition is one of *motor aphasia*. Motor aphasia may be divided into two varieties—subcortical and cortical aphasia. In the subcortical type the patient understands speech and writing perfectly and is able to write normally, but he cannot speak spontaneously or read aloud or repeat words when requested to do so. He can conceive words, but cannot express them. When, on the other hand, there is inability to conceive words, a lack of inner word-building power, then the case is one of cortical aphasia.

The gradations in the loss of the expressive factor may be very minute. A patient may sing a song, yet be unable to speak or write it. In a case described by Broca, the patient retained the power of using the word "three" only, and was obliged to make it do duty for all numerical concepts. Sometimes he can express his ideas in speech, but not in writing (agraphia). Motor aphasia is generally accompanied by paralysis, often transient on the right side, particularly the right arm. This is explained by the proximity of the inferior frontal convolution (Broca's speech area) to the motor area of the arm, and their common blood supply. The speech centre in right-handed persons is situated on the left side of the brain, and in the right side of the brain in left-handed individuals. This is a matter of education. It is no doubt true that after complete destruction of the left inferior frontal convolution the power of speech

may to a considerable extent be regained, and this may be due to powers residing in the right speech centre.

In sensory aphasia the perceptive factor in speech is deranged. In ordinary cortical sensory aphasia the patient cannot understand spoken or written language. He may talk incessantly but the series of words, correctly enunciated, have no connected meaning or may be a mere jargon not composed of known words at all. This condition is associated with lesions in two distinct regions of the brain. If the upper portion of the temporosphenoidal lobe is damaged, then the spoken word is missed, the written word is understood. This is word deafness. On the other hand, when the lesion lies in the occipital region then spoken words are understood and written words not at all. This is word blindness. Sensory, like motor aphasia, may exist in all degrees of completeness and both may exist together.

Weight of Brain.—Roughly it is three pounds, or about one-fortieth of the total body weight, and this ratio is greater than in the lower animals, with a few exceptions among the smaller birds and monkeys.

WEIGHT OF BRAIN IN GRAMS (TOPINARD)

Classes.	Males.	Females.
Macrocephalic	1925 to 1701	1743 to 1501
Large	1700 to 1451	1500 to 1351
Medium	1450 to 1251	1350 to 1151
Small	1250 to 1001	1150 to 901
Microcephalic	1000 to 300	900 to 283

In comparing brain weights, the method of removal of the encephalon should always be considered, since retention of pia and the fluids of the ventricles affects the result.

In *Boyd's method,* after the skullcap has been removed but the pia left intact, the hemispheres are sliced away in horizontal sections as far down as the tentorium. By means of a section passing in front of the corpora quadrigemina the remainder of the hemispheres is removed. The cerebellum, including the quadrigemina, pons, and bulb, is finally removed. Each portion is weighed separately. Sometimes the pia and the fluid within the ventricles are included in the weight of the brain, and sometimes not. Broca gives the following table for the *weight of the pia,* for normal males:

Twenty to thirty years	45 grams.
Thirty-one to forty-one years	50 grams.
Sixty years	60 grams.

The ventricles have a capacity of 26 c.c. of water.

In considering the weights of different brains, it is assumed that the proportion of nervous to non-nervous tissue is constant, so that different weighings may be compared. If this be the case, then the variations in weight may be due to greater size of the individual nerve elements, indicating a greater potential energy, or they may be due to a greater number of nerve elements giving rise to more possible pathways. A minute study of the proportional weights of different parts of the brain shows that variations due to sex, age, and stature are very constant, which is in harmony with the view that weight differences are due to the size of the nerve elements rather than to variations in their number. In the latter case brain weights would show independent variations in different parts of the encephalon.

All parts of the central nervous system of males are heavier than corresponding parts of females. The weight varies, in each, directly with the stature and inversely with old age. The brains of *criminals* do not differ in any marked way from those of ordinary hospital patients. *Insane* (excluding microcephalics) have no characteristic brain weight, except in such cases where a congestion of the brain has occurred, when the weight is markedly increased; on the other hand, insanity due to destructive changes of brain tissue is marked by a low brain weight. As a whole, individuals whose brains during the years of growth have been under favorable circumstances possess the heavier brains. In some degree the size of the brain bears a direct relation to the *intellect* of the individual, but this is not absolute. The depth of the sulci and the consequent size and complexity of the convolutions are a more efficient measure of the brain power. In the largest of the apes the brain of an adult animal is about the same in weight as that of a human infant at birth.

Weight of Cord.—The average weight of the spinal cord is about 26.67 grams, without the nerve roots, but the pia intact. It is probable that this weight varies, like that of the brain, with age, sex, and stature.

Growth of Brain.—At birth the brain weight is about one-third of what it will be at maturity. The increase is very rapid during the first year; quite rapid during the next seven or eight years; after this it becomes very slow. The maximum weight is attained in men between the fiftieth and sixtieth years; in women, between the fortieth and fiftieth years. A *premaximum* at thirteen to fifteen for males, and at about fourteen for females, indicating a too vigorous growth, seems to be an important cause of death at this age. The encephalon reaches maturity much sooner than the body as a whole. At the end of the eighth year, when the brain has almost completed its growth, the body has reached but a third of its mature weight. At birth the brain forms 12 per cent. of the total weight of the body, while in the adult it forms but 2 per cent., or even less.

It has been estimated that the cortex alone contains 9,200,-000 cell bodies, and that the entire nervous system must contain at least 13,000,000,000 cells. It is generally *agreed that in the human being the number is not increased after the third month of fetal life.* All subsequent increase in the mass of the brain is, therefore, due to an enlargement of individual cells. There is very little direct evidence for this in man. Kaiser has measured the diameters of the cells of the anterior horns of the spinal cord, and in this manner has determined an increase in size. In the frog there is a gradual increase in the number of fibers of the ventral and dorsal spinal nerve roots. The rate of increase is about 50 fibers for the ventral roots and 70 fibers for the dorsal roots for each gram increase in the weight of the frog. Moreover, the greatest number of medullated fibers is to be found in the ventral roots near the cord, and in the dorsal roots near the ganglion. This is explained by assuming the presence of undeveloped cells which gradually become mature, and in so doing push out their processes.

The *area* of the *cerebral cortex* which is exposed has about one-half the extent of that which forms the walls of the sulci. It has been shown that the fibers of the cortex are greater in number in middle age than in youth or old age. The *association fibers*, moreover, form three parallel systems. The deepest of these is first to become medullated, and the middle layer last.

The average *specific gravity* of the brain for males is about 1036.3, and for females 1036. The gray matter has about 81

per cent. of water, and the white matter about 70 per cent. The amount diminishes from birth to maturity. Between the fiftieth and sixtieth years the brain loses in weight in all parts, but the loss in the cerebral hemispheres is slightly greater than in other portions. The entire cerebral cortex diminishes in thickness with *age*, but more in motor than in sensory areas. In the cerebellum the branches of the arbor vitæ decrease in number and size; some of the cells are found to be shrunken, while the cells of Purkinje disappear altogether. In the cord, especially in the lumbar region, the cells become shrunken, pigmented, and degenerate; the supporting tissue is increased, and the walls of the bloodvessels are thickened. In paralysis agitans similar but more marked changes occur. With the advance of age the entire central nervous system breaks down into groups of elements, so that its powers are lost in an irregular and disjointed manner.

Fatigue.—When by voluntary contractions of the muscles of the index finger a moderately heavy weight is raised at regular intervals, it is found that the height of the contractions gradually decreases, so that in time the weight can no longer be lifted. If the effort is continued, it is found, in some people at least, that the power of contraction returns periodically to nearly its normal strength, so that a record of the contractions presents a series of waves. The *local feeling of fatigue* in this case is probably due, to a great extent, to the organs of muscular sense. An explanation of the *general fatigue* which may result is to be found in Mosso's experiment, in which he injected the blood of a fatigued animal into the circulation of a normal one, giving rise in the latter to all the symptoms of fatigue. It cannot be doubted that muscular activity gives rise to products, which are carried to the brain in the circulation. Lactic acid and the monophosphates of alkali metals circulated through a muscle produce in it all the characters of typical fatigue. Lactic acid, although formed in muscle, is, however, not alone responsible.

Blood Supply of Brain.—In general, the capillary network is closest in the gray matter or wherever any aggregation of cell bodies is to be found. Huber has demonstrated nerve fibers in the walls of the vessels of the pia, and Kölliker claims to have traced them to vessels of the nervous substance proper. *Vasomotor phenomena* of the brain have been demonstrated physiologically.

A general rise of arterial pressure causes the blood to flow more rapidly in the cerebral vessels, raises the venous pressure and also the *intracranial pressure*. To some extent, the latter is compensated for by a flow of cerebrospinal fluid through the foramen magnum into the vertebral canal. If the pressure continues to rise, the distention of the brain shuts off that outlet. Increase of pressure from now on impedes the circulation through the brain. It follows, therefore, that in pathological cases where trephining of the skull results beneficially the explanation may lie in a better blood flow.

The *metabolism* of the central nervous system is not very intense. This is readily understood when it is known that the cell bodies equal only 2 per cent. of the entire mass of the brain. The relative metabolism is less than that of muscles. During mental activity blood passes from the limbs to the head, as shown in cases where a defect of the cranial wall exists. During fatigue the brain becomes anemic, coinciding with a decrease in the force of the heart beat and of the tone of the abdominal vessels.

Sleep.—This phenomenon is one of many instances of the rhythmic activities of the central nervous system. From time to time all animals with a well-developed nervous system go to sleep, during which psychical activity is at its lowest point. To reach this condition, the most important favoring factor is an exclusion of all or most of the impulses from the central nervous system. In a well-known case of Strümpell, in which, from a complicated anesthesia, all sensory impulses were limited in their entrance to a single eye and a single ear, the patient could be put to sleep at will by closing the eye and stopping the ear. In addition, sleep has been attributed to the following influences:

1. Chemical influences.
2. Circulatory influences.
3. Histological influences.

Those who hold to *chemical influences* in the production of sleep, maintain that during normal activity of the body various substances are formed which are circulated in the blood and directly lessen the activity of the nerve cells or indirectly diminish the supply of blood in the brain. In the theories of *circulatory influences* a fatigue of the vasomotor centre is looked upon

as the cause of the anemia of the brain resulting in sleep. In the *third set of theories* sleep is supposed to be due to a separation of the dendrites of the brain cells due to an active contraction or to an intrusion of neuroglia cells between them.

During sleep the capability of the nervous system to transmit impulses is not entirely lost. The cerebral cortex is most affected, the spinal cord least. The close relation between dreams and external stimuli is well known, and it has been proved experimentally that vasomotor changes, induced by external stimuli, may take place without awakening the sleeper.

The period of *deep sleep* is short and falls within the first two hours after its onset. During this time the pulse and breathing are slower, the intestines and bladder are at rest, the output of carbon dioxide is lessened, and the consumption of oxygen still more so; metabolism is less vigorous and the temperature falls. The respiration is said to become thoracic in type, and to take on a more or less pronounced Cheyne-Stokes rhythm. The visual axes are directed upward and inward, but the *pupils are contracted.* The latter is peculiar, since an absence of light should bring about dilatation. This is connected perhaps with important actions taking place in lower levels of the brain.

Loss of sleep is more injurious than starvation. Dogs have recovered from a period of starvation of twenty days, but a loss of sleep of five days proved fatal. The body temperature fell 8° C. below normal and the reflexes disappeared. The red blood corpuscles first were diminished, but later increased in number. Postmortem examination revealed widespread fatty degeneration and cerebral hemorrhage.

In experiments made by Patrick and Gilbert, three subjects were observed for ninety hours while being deprived of sleep. The gain in weight which resulted was lost during the first sleep after the experiment. A decreased pulse rate and a lowered body temperature were observed. In general, there was a loss of all powers except in acuteness of vision, which was increased.

Hibernation.—This is connected closely with sleep, occurring periodically in many groups of animals and in a few mammals. It is characterized by a lessened metabolism resulting from a fall of the external temperature, and may be produced artificially in summer by cold. The heart beats very slowly and not very vigorously, while respiration is very slow and feeble.

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Nevertheless, the blood, arterial as well as venous, is bright scarlet in color, owing to the little oxygen consumed by the tissues. A hibernating dormouse has been observed to gain in weight, which was due entirely to an excess of oxygen taken in. Muscles and nerves remained irritable, and stimulation of the vagus produces a still further slowing of the heart beat.

Hypnotism.—This state is analogous to, but by no means identical with, sleep. It differs in a peculiar loss of voluntary control over the muscular powers; in frequent anesthesia and hyperesthesia; in the great clearness of psychical images, which may be forgotten, however, upon awakening, but are remembered in subsequent trances. In the lighter stages the mind sees clearly what is going on about it, which is not true in sleep. Finally, hypnosis is characterized by an extraordinary obedience to suggestions. The power of inhibition residing in the cerebrum, by which the mind is constantly controlling and arresting reflex movements, seems to be diminished if not absent. Verworn has shown that the so-called hypnotism in animals is not due to an inhibition from the cortex, since the phenomena are obtained easily in decerebrate individuals.

QUESTIONS ON CHAPTER XII

How may the central nervous system be divided?
What is a neuron?
How do the branches of nerve cells end?
What is the general function of the nervous system?
What are afferent, efferent, and central neurons?
What is a reflex act?
Describe the path of a simple reflex.
Discuss the phenomenon of inhibition.
Discuss the spread of impulses in the cord.
Name the afferent paths to the brain.
Name the efferent paths from the brain.
Discuss in detail the paths of motor and cutaneous impulses.
Describe the effects of removal of the spinal cord.
What is meant by the tonic activity of the cord?
Discuss the knee-jerk, its variations and reënforcement.
What is the time value of an average reflex action? For what reasons does it vary?
Distinguish between reflex time and reaction time.
Define personal equation.
Discuss the medical significance of some reflexes.
What is Babinski's sign?
Describe briefly the functions of all the cranial nerves.
Give the functions of the medulla oblongata.
What is a centre?

What views have been expressed with reference to the functions of the cerebellum?

What is the effect upon muscles of removal of the cerebellum?

What is Romberg's symptom?

Describe forced movements.

Give the connections of the cerebellum with the cord.

Describe the connections between the vestibular nerve and the cerebellum.

What connections exist between the cerebellum and the cerebral cortex?

Describe in detail the effects of ablation of the cerebrum.

Discuss the motor area of the cerebrum.

What is the path taken by motor impulses?

Distinguish between the paralysis resulting from injury to spinal or pyramidal neurons.

Discuss decerebrate rigidity.

Discuss the manner in which recovery from paralysis is brought about.

What is the location of the body sense area?

Trace the paths to the cerebral cortex followed by cutaneous impulses.

Give the location of the visual area.

Describe the effects of ablation of the occipital lobes.

Give in detail the path taken by visual impulses.

What is the location of the auditory area?

Trace, in detail, the paths taken by auditory impulses.

Locate the cerebral smell and taste areas.

Discuss the association areas of the cerebrum.

What is aphasia? How many types are there? Discuss each in detail.

What is the location of Broca's area?

Give a classification of brains with reference to weight.

Describe Boyd's method for weighing brains.

Discuss the significance of brain weights.

Describe briefly the growth of the brain.

Distinguish between general fatigue and a local feeling of fatigue.

What can be said of the blood supply of the brain?

Discuss the phenomena and the theories of the causation of sleep.

What are the effects of loss of sleep?

Discuss hibernation.

Discuss hypnotism.

CHAPTER XIII

THE SPECIAL SENSES

Sight.—The eye is a special organ by means of which certain rhythmic disturbances of the ether affect consciousness and produce the sensation of light. Among other functions that the eye serves are the determination of color, of distance, and of form. It consists of various adjustable refracting media, by means of which the rays of light are focussed properly on the retina, and of various muscles and accessory structures by means of which the eye is moved in different directions and is protected.

The muscles of the eye serve to move the eyeball through wide angles in all directions. When the *axis* of *vision* points straight ahead, the eye is in the *primary* position. If it moves from this position, so that the axis of vision rotates either about the transverse or vertical axis, then the eye is in a *secondary* position. All other positions are called *tertiary*. In order to understand clearly the nature of the image received by the eye, it is only necessary to review the images cast by a convex lens. If a double convex lens is taken and the image formed by a luminous object is noted, it is seen that it is an inverted image. Referring to Fig. 14, it will be seen that the rays originating at A will be twice refracted by the lens, once as they enter it and again as they leave it, so that all rays from A reaching the lens are joined at a. The same is true for B and b. Therefore, a screen placed at focus, F, will receive an inverted image, ab, of the luminous object AB. If the lens were more convex, the image would be formed nearer the lens; if the lens were flatter, the image would fall farther from the lens. Again, on the other hand, if the image is to be formed at a definite spot, the farther the object is from the lens the flatter the lens must be; and, *vice versa*, the nearer the object the more curved the lens must be,

With a double convex lens the image formed is real, inverted, and on the opposite side of the lens from the object. The *crystalline lens* is a double convex lens, and obeys the laws just described for other lenses. In addition, there are other refracting media in the eye—the *cornea,* the *aqueous,* and the *vitreous humors.* The crystalline lens is, however, the most important, as it possesses the power by virtue of the ciliary muscles of increasing or diminishing its curvature.

By *accommodation* is meant the power of changing the amount of curvature of the crystalline lens so as to throw the image of an object in exact focus on the retina whether the object be near or far from the lens. At the same time the pupil is expanded or contracted to admit the necessary amount of light. Thus, if an object be near the eye, in order to produce a sharp image

FIG. 14
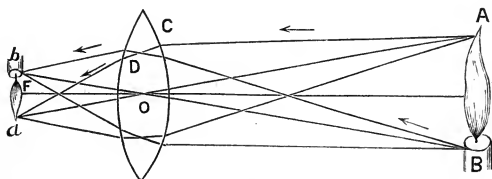
Formation of image by convex lens.

the lens is more curved, owing to the contraction of the ciliary muscle, and the *pupil* is *contracted.* If, on the other hand, the object be on the horizon, the ciliary muscle relaxes, the lens is flatter, and the *pupil* is *dilated.* Accommodation is an example of a voluntary act brought about by the action of the unstriped fibers of the ciliary muscle. The fact that most people must be assisted by visual sensations does not alter the fact that it is the result of the will. The *nervous path* of accommodation is through the anterior part of the nucleus of the third nerve in the floor in the third ventricle, the anterior bundle of the nerve root, the third nerve, the lenticular ganglion, and the short ciliary nerves.

Atropine paralyzes and physostigmine stimulates the ciliary muscle. Associated with accommodation for near vision there is, besides the contraction of the pupil, a convergence of the

axes of the eyes. The farthest point from the eye at which an object can be distinctly seen is called the *far point,* and the nearest point of distinct vision is the *near point,* while the distance between near point and far point is the *range* of accommodation. The near point is the shortest focus of the crystalline lens, and is usually about five or six inches.

Emmetropia is the normal eye—that is, an eye in which parallel rays or rays from objects at a distance are focussed upon the retina without an effort of accommodation. Such a distance for practical purposes is considered to be any point beyond twenty feet. Absolutely emmetropic eyes are not common.

Myopia, or near sight, is the term applied to an eye in which the rays from a distance are focussed in front of the retina and the image is blurred. Such an eye is permanently focussed for near objects (Fig. 15).

FIG. 15
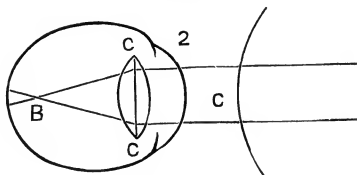
Myopic eye.

Myopia is produced in two ways—by the anteroposterior diameter of the eye being too great, or by the convexity of the lens being exaggerated. In either case the focus of the lens will fall in front of the retina. Myopia is corrected by the use of a concave lens, which diverges the rays and in this way prevents their coming to a focus too soon.

Hypermetropia, or far sight, is the reverse of myopia (Fig. 16). In this case the anteroposterior axis of the eye is too short, or else there is an abnormal flattening of the lens which does not allow accommodation for near vision. The result is that the image of an object near by is focussed behind the retina; but objects at a distance are clearly seen.

Hypermetropia is corrected by the use of a convex lens, which adds to the refractive power of the eye and the convexity can be increased for near vision.

Presbyopia is defective vision due to the loss of power in advanced years. The *elasticity* of the *lens* becomes less, and the convexity cannot be increased for near vision. The ciliary muscle may also be weaker and aid in the production of the error.

Astigmatism is a defect in the vision due to irregularity in the globe of the eye whereby the diameter in one plane is greater than in another. Thus, the cornea or the retina may be an uneven surface, and the image focus definitely in one part and falsely in another. In this condition vertical, variously oblique, and horizontal lines are not seen with equal distinctness. Astigmatism is corrected by the use of cylindrical or prismatic glasses, which have to be accurately adapted to the needs of each case. This error, if serious, usually accompanies other defects of vision.

FIG. 16
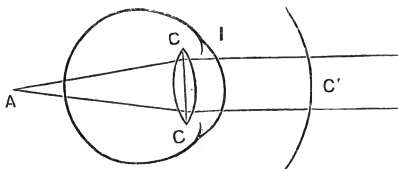
Hypermetropic eye.

Diplopia is the condition which results from a want of harmony in the action of the eyes, so that the image of each eye is perceived separately—that is, two images are seen. Diplopia is caused commonly by paralysis or spasm in one of the lateral straight muscles, which results in an abnormal position of the eyes. If the eyes are turned so that the axes of vision separate, the condition is known as *external strabismus*, or *squint;* if the axes are crossed, the result is *internal strabismus*, or *cross-eye*.

When a pencil of rays falls on a spherical, refracting surface, those at the periphery of the surface will be refracted more than those which lie near the axis, and will come to a focus sooner. This phenomenon is known as *spherical aberration,* and it exists ordinarily as an imperfection in the eye, where it is corrected largely by the greater refractive index of the centre of the lens, and partly as well by the fact that the iris cuts off the peripheral rays.

Contraction or *dilatation of the pupil* is a reflex act, and the afferent impulse is carried through the optic nerve, while the motor impulse comes through the third cranial nerve, acting from a centre just beneath the aqueduct of Sylvius and the corpora quadrigemina. An increase in the amount of light that comes to the retina causes a contraction of the pupil, and a decrease is followed by a dilatation. The pupil is controlled by fibers of the sympathetic and fifth cranial nerve which connect with the ciliary ganglion. Drugs are active in controlling the action of the iris. Atropine, both locally and internally, dilates the pupil; opium taken internally, and eserin applied locally, contract it.

If in obtaining an image of an object through a double convex lens the lens be too large, there will be seen around the image formed a halo of prismatic colors. This is called *chromatic aberration*, and is produced by an unequal refraction of light rays by the peripheral portions of the lens. The unequal refraction results in a dispersion of the light, so that it is broken up into the primary colors. This defect is remedied by putting a shutter in front of the lens, and so limiting the entrance of light to the central portions of the lens, where the index of refraction is constant. In the eye the iris acts as a shutter, thus making the image achromatic, but in some defective eyes where there is considerable fault in the focus of the image on the retina a visible band of color appears.

Under certain conditions a number of objects lying within the eye itself become visible. Of these *intra-ocular* images, the most common are known as *muscæ volitantes*. These are in the form of beads, streaks, or patches. They have an independent motion, which is increased by the movements of the eye. They are of greater specific gravity than the medium in which they are found, and are supposed to be the remains of the embryonic structure of the vitreous body.

Under normal conditions the *pupil appears* as a *black* spot. The reason for this is that the source of light and the retina lie in conjugate foci, so that any light which escapes absorption by the retinal pigment is reflected back whence it came. Therefore, the eye of an observer who views it from another direction will see no light coming from it. By means of an *ophthalmoscope*, however, a strong light is thrown into the fundus of the

eye, which upon reflection is viewed by an observer through an opening in the reflector. The fundus is seen to have a reddish background in which the retinal vessels are visible.

The most important structures of the retina are the *rods* and *cones*. They are closely packed on the outer surface, the rods over the greater part of the retina being the more numerous. They are cylindrical bodies of a transparent substance placed parallel to one another and perpendicular to the surface of the eyeball. The cones, which are modifications of the rods, are very similar to the latter, but do not reach the same level. These structures are connected through intermediate neurons with the fibers of the optic nerve. Where this nerve enters the retina, a little to the inner side of the most posterior point of the eyeball, there are no rods or cones, so that an image focussed at this point will be followed by no perception. This point is called the *blind spot.*

At the exact centre of the retina—that is, the most posterior point of the eye—there is a small yellow area (*macula lutea*) with a central depression (*fovea centralis*). Here none of the fibers of the optic nerve are to be found, but a great increase in the number of cones as well as an increase in their size. If the object looked at is focussed directly upon the fovea centralis, the image is seen with greatest clearness. In every-day life images are received upon the macula lutea, and rays of light entering the eye at an angle are focussed on some other part of the retina, and are not defined so clearly.

A retina which has been protected from the light for a time has a purplish-red color, due to a coloring matter termed *visual purple.* This is confined to the outer portions of the rods, and does not reach the cones. It is bleached by light, but restored by the pigment epithelium. The retina of a rabbit may be impressed with an image focussed upon it and then treated with a 4 per cent. solution of alum, which "fixes" it and prevents the restoration of the visual purple. Such a picture is called an *optogram.*

Vibrations of the ether form the normal stimulus for the retina, the rods and cones of which form, perhaps, the only structures of man that can supply the necessary conditions for the transformation of radiant energy into the energy of a nerve impulse. The ether vibrations vary widely in their

frequency, and only certain ones are capable of affecting the eye. The impulses they generate pass to the brain by way of the optic nerves, giving the sensation of light.

If the optic nerves are examined in a superficial manner, they will be seen to leave each eye and pass backward through the optic foramina until they reach the body of the sphenoids. Here they cross one another in the form of an X (optic chiasm), the fibers intermingling, and the right nerve apparently passing over to the left side and the left nerve to the right side. The posterior limbs of the X pass backward, and are called the optic tracts. The optic tracts in their course curve around the crura cerebri to terminate in the nerve cells of the pulvinar, anterior quadrigemina, and external geniculate bodies. From these, fibers, called the *optic radiations*, pass backward to terminate in the cells of the cortex of the posterior part of the occipital lobes. A closer examination of the optic nerves will show that each consists of two bundles of fibers laterally placed. The inner set of fibers comes from the inner half of the retina; the outer bundle comes from the outer half of the retina. If these bundles are traced to the optic chiasm, it is noted that the inner bundles decussate and pass to the opposite side of the brain. Thus the left pulvinar, left anterior quadrigeminate, and external geniculate bodies receive fibers from the inner half of the right eye, and from the outer half of the left eye. The commissure of Gudden, which connects the internal geniculate bodies, probably plays no part in vision. When an image is properly received on the retina, it excites the rods and cones to activity. When the impulses reach the basal ganglia, the sensation of light is not aroused. Light is not perceived until the impulses reach the cortex of the cerebrum. The pulvinars, the external geniculate bodies, and the anterior quadrigemina form the *primary vision centre*.

The character of the sensations aroused depends upon three modifications of light:

1. Color, which depends upon the rate of vibration of the ether waves.

2. Intensity, which depends upon the energy of the vibrations.

3. Saturation, which depends upon the amount of white light mixed with light of one wave length.

It is easily demonstrated for man that luminosity is recognized more easily than color, and this probably holds true for all organisms. Colored objects appear colorless when the light is too feeble, and if the light is increased in intensity the colors appear, but as it becomes too strong there is a tendency for all colors to pass into white. This is most noticeable in the yellow. Different regions of the retina vary also in their power to distinguish colors. Red is lost at a short distance from the macula lutea, while the violet is lost only at the borders of the retina.

Stimulation of the retina is followed normally by a latent period, then by a period during which the effect of the excitation reaches a maximum; from the maximum there is a slow decline in the effect, which is analogous to fatigue, and when the stimulation has ceased there is an after-effect which slowly passes away. When a very bright object is looked at for some time, the impression upon the retina lasts for a considerable interval after the excitation has ceased. This is called the *positive after-image*. Both form and color are visible. The latter generally passes through a series of colors—green, blue, violet, purple, and red—before it disappears. The *negative after-image* depends upon fatigue of the retina, and differs from the positive after-image in that its color is the complementary of that of the object. The effect produced by an object upon the retina depends in part upon the amount it has been fatigued by previous impressions. This makes the field of vision appear darker near a light area and lighter near a dark area than it really is, while color is so modified by the neighboring field that it appears the complementary of the latter.

Ordinary white light, if decomposed, is resolved into the seven primary colors—violet, indigo, blue, green, yellow, orange, and red. Each of these primary colors has a different wave length. Colors other than the seven primary colors are the result of the mixture of two or more of the primary colors in various proportions. Nothing is known of the manner in which the rods and cones are made to vibrate by ordinary images, nor as to the nature of the process by which the different color effects are conveyed by the optic nerve. The different *color theories* assume that there are different substances in the retina capable of responding to different wave lengths of light (comparable to a photochemical process). Red, green, and

violet are the fundamental colors, and all others can be made by combinations of these three. Working on this basis, *Young and Helmholtz* assumed three chemical substances in the retina capable of responding to the three fundamental colors. *Hering* assumed three substances corresponding respectively to white or black, red or green, and yellow or blue light. In this theory the white, red, and yellow rays are katabolic in their effects on their individual recipient substances, while black (absence of light), green, and blue are anabolic, thus having an antagonistic effect. *Mrs. Franklin* assumes in her theory that in early life the eye possesses no color perception, but merely the power of perceiving luminosity, *i. e.*, distinguishing between white and black. The substance responding to luminosity is called gray-perceiving. As the development progresses, some of the gray is differentiated into a blue- and a yellow-perceiving substance. The yellow-perceiving substance is still further differentiated in the course of development into a red- and a green-perceiving substance; thus:

Gray.

Blue.

Yellow.

Green.

Red.
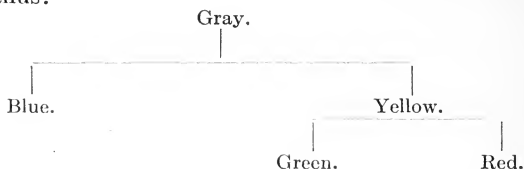
Many objections have been raised against each of these theories, but Mrs. Franklin's is so far the best, and explains more readily the causes of *color blindness.* According to the theories of *Helmholtz* and *Hering,* color blindness is due to an absence of of one or more of the fundamental color-perceiving substances. *Mrs. Franklin's* theory assumes a lack of full development or complete absence of development of gray substance. If the development should cease after the blue- and yellow-perceiving substances have been formed, the individuals would be capable of distinguishing the blues and yellows, but could not recognize reds and greens. Clinically, such cases often are met with. Males are far more likely to be color-blind than females (16 to 1). Only 1 woman in 400 is color blind. The reason for this is partly at least that the development of the gray-perceiving substance is favored by practice and color education.

The retina is capable of judging the *size of objects* in two dimensions only, *i. e.*, in the plane perpendicular to the axis of vision. The *perception of distance* is closely connected with the fact that the size of the image formed upon the retina varies with the distance. Besides, the distinctness with which objects are seen influences the judgment of distance, because when indistinctly seen, objects are supposed to be farther away. Again, the judgment of distance is further aided by the sense of effort required in accommodation, and also by the change of position of an image on the retina when the eye is moved. The latter depends upon the fact that the change in the position of the image is inversely proportional to the distance of the objects. Many circumstances affect the accuracy of the spatial judgment of the retina. One of these is *irradiation*. All brightly illuminated objects appear larger than others of the same size.

Although there are two eyes, each of which furnishes an impression, only one object is perceived. In abnormal positions of the eye the two impressions can be made recognizable. Ordinarily, therefore, the images of objects fall on *corresponding points* of the retina. A point on the right side of one retina has its corresponding point on the left side of the retina of the other eye. When the images fall on corresponding points, they are blended into one perception. *Binocular vision* affords a method of judging the solidity of objects, since the image of any object falling on one eye cannot be exactly like that which falls on the other. Thus, the perceptive faculties can judge more correctly of the form and distance of an object.

From the laws of optics it is known that the image formed on the retina is an *inverted image* of the object. Yet it is perceived in its upright position. This is the result of lifelong habit. A baby sees an object; the next step is to touch it; by practice the child finds out which is the top of the object through the touch perception. Very speedily the brain learns to make the correction. It is an act of mental and not physical origin. Thus, objects which are projected upon the left of the retinal surface look to be, as they really are, on the right of the body; and so with all the directions.

Clearness of vision depends upon the space between the cones in the point of clearest vision, the fovea centralis. It has been calculated that an object must subtend an arc of at least 60

to 70 seconds in the field of vision to be clearly seen. Such an object makes an image $\frac{1}{12000}$ of an inch on the retina, and this is about the distance between the cones at the macula lutea. In order that two points may be distinguished, they must be separated at least this amount.

Hearing.—It may be accepted as a well-defined physiological fact that the nervous structures of the cochlea form that organ by which musical sound and noise of all kinds are converted into nerve impulses. The sound waves of the air, which originate in vibrating bodies, are gathered together by the concha, carried into the external auditory canal, and vibrate against the membrana tympani. The latter takes up the vibrations and transmits them through the chain of ossicles to the stapes in the fenestra ovalis. The stapes imparts its motion to the perilymph of the vestibule. There is now set up in the perilymph a fluid wave that travels in all directions. It passes along the scala vestibuli to the apex of the cochlea, then through the aperture of communication with the scala tympani down the latter until it expends itself against the membrane of the fenestra rotunda. In its passage the fluid vibrates against the membrane of Reissner and the basilar membrane, and this sets up similar vibrations in the endolymph of the canalis cochlearis. The fluid wave in the canalis cochlearis is in a position to irritate the hair cells of the *organ of Corti*. These cells seem to be able to respond to particular tones by their sensitiveness to certain rates of vibration. But the fact that the organs of Corti are absent in birds which evidently are capable of appreciating musical tones shows that they are accessory and not absolutely essential.

The branch of the eighth nerve, having received its impulses from the cells of the organ of Corti, transmits them to the centre under the acoustic tubercle in the floor of the fourth ventricle; thence fibers pass by means of the trapezium in the pons to the opposite side, and through the lower fillet of that side to the posterior quadrigeminal body, whence by means of the brachium, internal geniculate body, optic thalamus, and internal capsule, they proceed to the cortex of the superior temporal convolutions.

By *subjective hearing* is meant sounds that are heard distinctly and yet are not produced by physical sound waves from the

exterior, nor are they hallucinations. They may be due to disturbances of the auditory apparatus or to abnormal conditions of surrounding organs. Thus, buzzing or ringing in the ears may result from the hyperemia of the parts and the increased rush of blood, or from disease in the auditory nerve or some other portion of the apparatus. Hallucinations are purely creations of a disordered brain.

Musical sounds are distinguished by the mind by three factors —loudness, pitch, and quality. Every musical tone is produced by a succession of regular alternate rarefactions and condensations of the air. It is their *periodicity* which makes them musical, otherwise they are known as noises. The range of musical notes that can be appreciated by the human ear is about seven octaves. There are about 3000 hair cells in the organ of Corti, and it is easily seen that this would allow an enormous capability to differentiate sounds and musical tones. This corresponds to a range of from 40 to about 4000 vibrations per second. The range of *audibility*, on the other hand, is about eleven octaves, or from 16 to 38,000 vibrations per second. With less than 16 vibrations per second the ear perceives only separate shocks, while with more than the larger number the sensation of sound is not produced.

The *distance* and *direction of sounds* are not perceived directly, but are estimated by their loudness and quality combined with reasoning from past experience. When one ear is totally deaf, all sounds seem to originate from the side of the healthy ear. When the eyes are closed, a sound directly overhead is imperfectly localized, but seems to come from a point ahead and above the person. The quality as well as the loudness of the sound varies with the distance from its source, because the lower tones die away first, making the overtones more prominent. This is taken advantage of by *ventriloquists*, who, by modifying the intensity and quality of the voice, produce an imitation of the effect of distance. The ear is capable of appreciating very small intervals of time; 132 auditory impulses per second are heard separately, while in the eye all above 24 per second are fused together.

Sense of Equilibrium.—By sense of equilibrium or equipoise is meant a state of the body in which all the muscles are under control so as to resist the effect of gravity whenever

necessary. It is of the greatest importance to animals, and therefore several mechanisms share in its performance. It is brought about by sensory impulses coming from many sources, and the sum total of the sensations involved constitutes the *sense of equilibrium*. Every known sensation probably contributes to the maintenance of equilibrium, but certain structures in the ear, known as the semicircular canals, form the main source. When the canals are injured in any way, the animal sprawls on the ground, holds its head in an unnatural position, makes peculiar forced movements, etc. The effect varies with the number and the position of the canals operated upon, and ranges from simple unsteadiness of gait to complete incoordination. These results are explained as being due to increased or decreased pressure of the endolymph on the cristæ acusticæ of the ampullæ of the semicircular canals. The latter are situated in the three dimensions of space, and rotation of the body in any direction can be judged quite accurately as to direction and amount. Rapid rotation in one direction is, after its cessation, often followed by a sensation of rotation in the opposite direction. Excessive rotation leads to dizziness, but in deaf mutes dizziness is difficult to produce on account of the imperfect development of the ears. Diseases which alter the pressure in the canals lead to vertigo and incoördination. The semicircular canals in themselves, however, are not sufficient to preserve complete equilibrium.

Smell.—The special olfactory mucous membrane is situated in the upper part of the nasal cavity, away from the direct current of the inspired air. The rod cells which it contains are connected with fibers that are part of the olfactory nerve and constitute the sensory nerve endings. Substances that excite the sense of smell are in a fine state of division, or in a gaseous state, and are brought into contact with the rod cells by rapid but short inspiratory movements. They are perceived best when the air is at the body temperature. The substance producing smell is probably taken into solution in the moisture covering the olfactory membrane. In the lower animals the sense of smell plays a very important part, and it is probable that all animals give out characteristic odors by which they recognize one another. The sense of smell is, therefore, highly developed, which is not the case in man. The distri-

bution of the olfactory nerves is much wider and the cerebral development correspondingly greater in some animals than is the case in man, where, however, the range of susceptibility is wider. The variety of odors and the very minute quantity of the substance required to produce smell are wonderful. The most delicate analysis may fail to show traces of the substances which can be appreciated by the sense of smell. For instance, 0.000000005 of a gram of oil of peppermint in 1 liter of water can be detected. Some odors, like musk, are pleasant perfume to some, while to others they are unendurable. The *acuteness* of the sense of smell varies in different persons, and this may apply to certain odors only. Like the sense of touch and other senses, it can be developed by practice. Often in cases of mental disease there are hallucinations of smell.

The *olfactory nerves* arise from a mass of gray matter lying beneath the anterior lobe of the brain upon the cribriform plate of the ethmoid bone. This is the olfactory bulb, and is connected by the olfactory tract with the cerebrum. Each *olfactory tract* arises from the cerebrum by three roots, two of which are composed of white matter and the third of gray matter. By these it is connected with the olfactory centres. The perceptions of the olfactory nerve and of the nerves of touch of the nose often resemble each other, and some stimuli affect both nerves. The *common sensibility* is evoked by such substances as are irritating or acrid—ammonia gas has no odor, but it stimulates the mucous membrane of the nose. The relation between the two kinds of perception is lost, and the smell of ammonia or of alcohol is spoken of when it is not olfactory, but a sensory perception.

Taste.—The sense organs concerned in taste, the taste buds, are located on the upper surface and sides of the tongue, the anterior surface of the palate, and of the anterior pillars of the fauces. Those of the posterior third of the tongue are connected with the *glossopharyngeal nerve*, while those of the anterior part of the tongue are connected with the *lingual* and *chorda tympani* nerves. Taste perceptions are modified by simultaneous olfactory sensations, so that it is difficult to distinguish between an apple and an onion when the nostrils are closed. The *intensity* of taste increases with the area stimulated, and is greatest when the stimulating substance is at the temperature

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of the body. Taste depends upon the concentration of the solution. There is evidence that the sensation may be divided into *four primary ones*—bitter, sweet, sour, and salt, with *special nerves and end organs* for each. Thus, the tip of the tongue perceives acids acutely, sweets less, and bitter substances hardly at all. Saccharin appears sweet at the tip of the tongue and bitter at the base. The fungiform papillæ scattered over the surface of the tongue were tested with succinic acid, quinine, and sugar. Out of 125, 27 did not respond at all, showing that they were devoid of taste endings; 12 reacted to succinic acid alone; 3 to sugar alone; while quinine affected them all. An extract of a tropical plant has been found to paralyze the sense endings for sweet and bitter substances. Cocaine abolishes the sensibility of the tongue in the following order: (1) general feeling; (2) bitter taste; (3) sweet taste; (4) salt taste; (5) acid taste; (6) tactile perception.

The tongue has a highly developed sense of touch, temperature, pressure, and pain, which aid the accuracy of speech, mastication, and deglutition. Some aromatic substances leave an impression of their taste, called an *after-taste*, and when tasted in rapid succession a number of times the appreciation of their flavor is lost.

Cutaneous Sensations. — A specialized peripheral organ for the reception of an external impression, an afferent nerve, and the brain for the perception of the sensation, constitute an organ for sensation. It is by means of impressions so received and conducted to it that the mind is able to control the body, and to take cognizance of the external world. Cutaneous sensations include the sense of touch, temperature, and pain. *Touch* is due to sensory nerve endings in the skin and mucous membrane. The nails and teeth are peculiarly involved in the sense of touch, and also the hair in certain regions, *e. g.*, the eyelashes. The relation between the strength of the stimulus and the resulting sensation is expressed by *Weber's law:* "*The amount of stimulus necessary to provoke a perceptible increase of sensation always bears the same ratio to the amount of stimulus already applied.*" This law is only approximately correct for small and for large weights. Fechner's "*psychophysical*" *law* attempts to express the relation more exactly: "*The intensity of sensation varies with the logarithm of the*

stimulus," *i. e.,* the sensation increases in arithmetical, while the stimulus increases in geometrical proportion.

Different areas of the body vary in their power of discriminating pressure differences. The forehead, lips, and temples appreciate an increase of $\frac{1}{40}$ to $\frac{1}{30}$; but the head, fingers, and forearm can appreciate a stimulus only when increased from $\frac{1}{20}$ to $\frac{1}{10}$ of its previous intensity. When two equal weights of different expanse press upon the skin, the larger appears the heavier. A weight pressing upon the skin leaves an *after-sensation,* so that the intervals between successive applications of stimuli to touch endings cannot be less than $\frac{1}{610}$ of a second if they are to give separate sensations. If the impressions follow at a more rapid rate, they will be fused together into a continuous sensation.

Touch sensations are *localized, i. e.,* they are referred to the right portion of the body where the stimulus is applied. This power is acquired early in life and the sensations of touch are correlated with those of sight and those arising from muscles, so that each area of the skin acquires a "*local sign.*" The power and fineness of localization differ greatly for different portions of the skin. The following table is taken from Kirke's *Handbook:*

TABLE OF VARIATIONS IN THE TACTILE SENSIBILITY OF THE DIFFERENT PARTS[1]

Tip of tongue	$\frac{1}{24}$ inch
Palmar surface of third phalanx of forefinger	$\frac{1}{12}$ "
Palmar surface of second phalanges of fingers	$\frac{1}{6}$ "
Red surface of under lip	$\frac{1}{6}$ "
Tip of the nose	$\frac{1}{4}$ "
Middle of dorsum of tongue	$\frac{1}{3}$ "
Palm of hand	$\frac{5}{12}$ "
Centre of hard palate	$\frac{1}{2}$ "
Dorsal surface of first phalanges of fingers	$\frac{7}{12}$ "
Back of hand	$1\frac{1}{6}$ "
Dorsum of foot near toes	$1\frac{1}{2}$ "
Gluteal region	$1\frac{1}{2}$ "
Sacral region	$1\frac{1}{2}$ "
Upper and lower parts of forearm	$1\frac{1}{2}$ "
Back of neck near occiput	2 "
Upper dorsal and midlumbar regions	2 "
Middle part of forearm	$2\frac{1}{2}$ "
Middle of thigh	$2\frac{1}{2}$ "
Midcervical region	$2\frac{1}{2}$ "
Middorsal region	$2\frac{1}{2}$ "

[1] The measurement indicates the least distance at which the two blunted points of a pair of compasses could be separately distinguished.—E. H. Weber.

Tactile areas have, in general, an oval form, with the long axis parallel to the long axis of the portion of the body investigated. These areas are not indicative of the distribution of certain nerves. The important factor in the separation of two points that are stimulated is not that two different nerves shall be stimulated, but that there must be a certain number of unstimulated points between those stimulated.

The sense of touch can be greatly educated and specialized. The reading of raised letters by the blind is an example. Improved touch discrimination, attained by practice upon the skin of one arm, is accompanied by an improvement in the corresponding area of the other arm, but not of any other areas of the body. This shows that the localizing power lies within the central system.

The skin is an organ for the detection of temperature changes, and its power in this respect varies in different portions of the body. The intensity of the sensation depends upon the area stimulated. There is very little doubt that there are two *distinct temperature nerves*, which serve respectively for the appreciation of heat and cold. The areas to which the nerves are distributed can be located in the skin as cold and heat points. Temperature sensations are not accurate; they are only relative —that is, the temperature of various things is inferred from the temperature of the skin and its habitual surroundings. It is related that Arctic explorers have found the water warm when swimming in pools on icebergs, and a drop of mercury at 80° F. is said to feel cold in the tropics. A more simple illustration is that of immersing one hand in water at 40° F. and the other in water at 120° F., and then plunging both into water at 80° F., when one hand will feel hot and the other cold. During a chill the temperature of the body is often very high, and yet the sensation is that of cold.

Common Sensation.—By *common sensation* is meant that state of mind, more or less definite, by which the condition and position of the body at any moment are known. Such perceptions cannot be located distinctly in any organ or set of organs, as, for instance, hunger, thirst, etc. Besides these there are some sensations which involve certain organs which must be classed under this head; thus, inclinations to cough or to sneeze, to vomit, defecate, and urinate. Many of these

sensations occupy the border line between common sensibility and the special sense of touch, such as tickling and itching. Pain points are separate from pressure points and are more numerous. More than 100 are found to every square centimeter of the skin, and they require 1000 times as great a stimulus for their excitation as do the pressure points.

Hunger and *thirst* are peculiar sensations, which ordinarily depend partly on local and partly on general causes. Local causes of hunger and thirst are an empty stomach and certain conditions of the mucous membrane. These sensations are felt largely as the result of habit, and depend thus upon the condition of secreting and absorbing mechanisms.

By taking a body in the hand and rasing it, a sense of resistance is felt in the muscles, by the intensity of which the weight of the body can be determined more accurately than by the pressure sense alone. This is called *muscular sense*. It is developed to an exceedingly fine degree in some occupations; for example, postal clerks detect overweight letters with wonderful accuracy and quickness. Muscular sensation is allied closely to touch sensation. It is due to the inflow of sensory impulses which indicate the tension to which the muscle has been subjected. The latter view is corroborated by the existence of sensory endings, the *muscle spindles*, in muscles and tendons.

QUESTIONS ON CHAPTER XIII

What are the functions of the eye?
Give the essential parts of the eye.
What are primary, secondary, and tertiary positions of the eye?
How is an image formed on the retina?
Discuss accommodation.
Discuss the effect of drugs on accommodation.
Give the nervous mechanisms of accommodations.
Define near and far points and the range of accommodation.
What is an emmetropic eye?
Discuss myopia and hypermetropia.
What are presbyopia and astigmatism?
Discuss diplopia of the eye.
Define spherical aberration and chromatic aberration.
Give the nervous mechanisms that control the iris.
Discuss intra-ocular images.
Why does the pupil appear black?
What is an ophthalmoscope?
What are the most important structures of the retina?
What are the blind spot, macula lutea, and fovea centralis?

What is the visual purple?

How may an optogram be obtained?

What supplies the normal stimulus to the retina?

Give the course of the optic fibers.

What constitutes the primary vision centre?

Upon what physical conditions does the sensation of light depend?

How can it be shown that luminosity is recognized more easily by the eye than color?

How do different portions of the retina vary in their power to distinguish color?

Give the various phases of the activity of the retina when stimulated.

Distinguish between positive and negative after-images.

What is irradiation?

What is the relation of color to white light?

Discuss the color theories.

How is color blindness explained?

What is the proportion of color blind in men and women? What reason can be given for this?

Discuss the perception of distance.

Discuss binocular vision.

Discuss the correction for the inversion of the retinal image.

Upon what does clearness of vision depend?

Where are the physical vibrations of sound transformed into nervous impulses?

How do the sound waves of the air reach the organ of Corti?

Are the organs of Corti absolutely essential to the appreciation of musical tones?

How are the impulses conveyed from the ear to the brain?

What is subjective hearing and its causes?

Upon what factors do musical sounds depend?

How do noises differ from musical sounds?

What is the musical range of the ear?

What is the range of audibility of the ear?

How is the distance of sounds estimated?

Discuss the power of the ear to appreciate small intervals of time.

What is meant by equilibrium of the body?

How is the sense of equilibrium brought about?

What is the effect of injury to the semicircular canals of an animal?

What proof is there that the semicircular canals aid in preserving equilibrium?

What is the situation of the olfactory mucous membrane?

What is the condition of substances that excite smell?

What is the importance of smell in the lower animals?

Give instances of the delicacy of the power of smell.

Give the course of the olfactory fibers.

Discuss the relation of common sensibility and smell.

What is the location of the sense organs of taste?

What are the nerves of taste?

What is the relation of smell to taste?

Does taste depend upon concentration or on the quantity of the stimulating substance?

How is taste divided?

Give evidence of special end organs for each division.

How does cocaine affect the sensibility of the tongue?

What is the function of the tongue?

What is an after-taste?

What are the organs of cutaneous sensation?

What sensations are included in cutaneous sensations?

Give Weber's and Fechner's laws.

Discuss the discriminating power of different parts of the body to pressure.

What interval must elapse between touch stimuli in order that they may give separate impressions?

Discuss the localization of touch sensations.

What factor determines the recognition of two points of the skin stimulated simultaneously?

Discuss the situation of touch areas.

What fact shows that improved touch discrimination is a central phenomenon?

Discuss temperature sensations.

What is a common sensation?

Discuss the sensations of hunger and thirst.

What sensations are on the border-line between common sensation and special sensation?

What evidence is there for separate pain points in the skin?

What is meant by the muscular sense?

To what is muscular sense due?

CHAPTER XIV

REPRODUCTION

REPRODUCTION is a process by means of which life is perpetuated because the existence of individuals is limited. There are two methods of reproduction—the *asexual* and the *sexual*. The former is the more primitive form, and is restricted to the lower organisms. It is not difficult to conceive a reason for reproduction in cells, for as the mass of living matter increases, its volume increases as the cube, while its surface increases only as the square. There will finally result, therefore, a condition in which the absorptive surface is too small for the amount of living matter, and a division will cause a relative increase of surface. *Sexual reproduction* is derived probably from the asexual method, and consists in the union of male and female elements. The most primitive examples are to be found in some of the unicellular organisms where there is a fusion of the two sexes, known as *conjugation*. The resultant mass divides and so produces its offspring. In somewhat more highly differentiated forms there are simply an exchange and a fusion of nuclear matter. In the higher animals there is a fusion of nuclear matter of two individuals brought about by the production of two kinds of sexual cells—*ova* and *spermatozoa*. In some animals, like the worms, both sexual elements exist in the same individual, but this condition is found only abnormally in the highest animals. Here the sexes present wide anatomical, physiological, and psychological differences. These differences fall into two groups—*primary* and *secondary*. The primary sexual characters are the most pronounced, and consist of those pertaining to the sexual organs and their functions. The secondary sexual characters are accessory to the primary ones, and include the differences in voice, growth of hair on the face, the mammary glands, etc., in man and woman.

The sexual cells differ widely in appearance. The spermatozoön consists of an elliptical head, a short middle piece, and a tapering tail. It is undoubtedly a cell which arises from a testicular cell known as the *spermatocyte*. The latter divides into four *spermatids* which grow directly into spermatozoa. It is important as well as interesting to know that the number of chromosomes in the head of the spermatozoön is one-half the number normally present in the body cells of the individual. The spermatozoön is adapted to vigorous activity. It seeks the ovum by means of the movements of its tail, which is lashed from side to side, causing it to progress and at the same time to rotate. The rapidity with which it moves is from 1.2 to 3.6 mm. per second. Spermatozoa will live in the male genital passages for months, and they probably will live in the female for a long while, but the exact time is not known. They are produced in large numbers. One estimate puts the production at 226,257,000 per week. The spermatozoa are contained in a fluid which comes from the testes partly, but chiefly from accessory sexual glands—the seminal vesicles, the prostate gland, and Cowper's glands. Together these constituents form the *semen*, which may be described as a whitish viscid fluid with a characteristic odor. The amount passed at a time is from 0.5 to 6 c.c. In some animals it contains fibrinogen, which enables it to clot within the female passages, thus preventing escape of the spermatozoa.

The *ovum* in its perfected state as it leaves the *Graafian follicle* is found to be a minute globular cell containing a nucleus and nucleolus as well as a cell membrane. It undergoes a process analogous to what takes place in the formation of a spermatozoön, which is known as *maturation*. It begins as the ovum is leaving the ovary, and consists of a karyokinetic division of the nucleus twice in succession. With each division half of the nucleus is extruded together with a small amount of protoplasm as the *polar bodies*. The first polar body usually divides into two parts, making three polar bodies, all of which degenerate. As the result of these divisions the ovum has left one-half of the number of chromosomes of a body cell. The union of the nuclei of ovum and spermatozoön restores to their original number the chromosomes of the species. Ova are developed within specialized cavities of the ovary lined by

epithelial cells, known as Graafian follicles. A Graafian follicle moves toward the surface of the ovary, ruptures, and discharges the ovum, giving rise to the process of *ovulation*. This is in most animals a periodic phenomenon, and in woman probably begins at puberty with the first menstruation and continues until the climacteric. Cases of pregnancy at the ages of seven, eight, and nine years show that it may occur very early. After the ovum has been set free from the ovary it in some unknown manner reaches the Fallopian tubes. It is possible that in woman, as has been observed in some animals, the fimbriated ends of the tubes clasp the ovaries when the eggs are discharged. The cilia lining the tubes gradually carry the egg toward the uterus, which it reaches in from four to eight days.

Impregnation or *fertilization* usually takes place in the tubes because the cilia, while they carry the ovum in one direction, act as a guiding stimulus to the spermatozoa, which move in the opposite direction to meet the ovum. In case the ovum is fertilized it passes on to the uterus, where it is retained and develops to the end of the embryonic period.

The uterus is active monthly in that it discharges a bloody, mucous liquid through the vagina. This is called *menstruation*. Some days before the flow the mucous membrane of the body of the uterus begins to thicken by the growth of its connective tissue, and by the engorgement of its bloodvessels until it is from two to three times its normal thickness. The swollen capillaries become ruptured and the epithelial cells undergo a degeneration. Usually only the superficial portions of the mucous membrane are involved, and those cases where it is removed to its deepest layers are very likely pathological. The flow continues for four days or more, during which 100 to 200 c.c. of blood are lost. The latter is slimy with mucus, does not coagulate, contains disintegrated tissue, epithelial cells, and has a characteristic odor. Menstruation is accompanied by many other symptoms. The ovaries and breasts are congested, dark rings form about the eyes, mental depression often exists, skin and breath have a characteristic odor. The intermenstrual period exhibits a gradual increase in nervous tension and metabolic activity, manifested in an increased production and excretion of urea, in a higher temperature, and an increase

in the strength and rate of the heart beat. These reach their maximum a few days before the menstrual flow, and then undergo a rapid fall, reaching a minimum with the cessation of the flow. The first menstruation is an index of puberty, and occurs in temperate climates at the age of from fourteen to seventeen. The time varies with the climate, food, growth, environment, etc. Occasionally menstruation may be entirely absent in otherwise normal women. The removal of the ovaries puts an end to further menstruation. Its cessation at the age of forty-five to forty-eight marks the *menopause* or *climacteric*.

The meaning of menstruation has been much discussed. In the lower mammalia reproduction is limited to seasonal periods, which are characterized by sexual excitement, congestion and swelling of the external genital organs, and a uterine discharge. During the remainder of the year sexual excitement is absent. These periods of excitement are known as *rut* or *heat*. Domestication with its regular food supply and care has increased productiveness by rendering the reproductive periods more frequent. This has taken place in like manner in the human, but has progressed farther in that woman during the menstrual flow has largely lost sexual desire. According to Pflüger, menstruation is a preparation of the uterine surface for the reception of the impregnated egg. An alternative view is that menstruation takes place because the ovum has not been fertilized. The nutrition of the uterus seems to be intimately dependent upon the ovaries through an influence exerted by a hormone formed by the corpus luteum. In monkeys, menstruation takes place after the ovaries have been transplanted, but the flow stops when the transplanted ovaries are removed from the body. It has also been stated that in a young woman suffering from amenorrhea a regular flow appeared after the transplantation of an ovary from another woman into her uterus. The influence of the ovary on the formation of the decidua has been shown in the artificial production of deciduomata. If a number of incisions are made into the uterus of a rabbit within a certain interval after the estral period, a structure with the histological characters of the decidua develops at each wound. Ovulation seems indispensable to the production of this phenomenon.

While in the uterus the growing fetus derives by far the greater part of its nourishment from the mother by means of the *placenta*.

*Here the circulation of the child is brought into intimate relation to
that of the mother, but they are nevertheless separated by four layers
of cells.* Although there is no direct communication, there is an
exchange of material between the mother's blood and the fetal
blood. The mother's blood furnishes to the fetal blood food and
oxygen, and in turn removes the carbon dioxide and excremen-
titious material which the fetus must lose. The placental cir-
culation supplies the place taken in after life by the alimentary
and respiratory tracts. When the placenta is expelled, a part
of the maternal tissue is left behind, and there is, of course, a
loss of blood contained in the uterine sinuses, but the general
balance of the circulation is not disturbed at childbirth. The
reason for this is the oblique entrance of the placental vessels.
They enter the sinuses at an angle and are therefore compressed
by the muscular tissue of the uterus in its contracted state.
There are two distinct types of circulation in fetal life—the
vitelline and the *placental* circulation. In both types the blood
is driven on by the heart, the essential difference being the
site where the fetal blood is enriched. The vitelline circulation
precedes that of the placenta, and as soon as the latter is formed
the former disappears. The vitelline circulation in the human
is very short-lived.

The placental circulation presents two prominent features in
which it differs from adult circulation:

1. Modifications are necessary in the heart and great blood-
vessels in order that the blood may not enter the lungs.

2. In the circulation through the liver the veins are modified
so as to allow for the return of placental circulation.

The *course* of the *fetal circulation* is as follows: The fetal
blood, purified and enriched in the placenta, passes by the
umbilical vein in the umbilical cord to the under surface of the
liver; here the vein divides into two parts. One portion of the
blood enters the liver substance, and after traversing its cap-
illaries is poured out by the hepatic veins into the inferior vena
cava. The other portion of the blood passes directly from the
umbilical vein to the inferior vena cava by means of a blood
channel, the ductus venosus. The blood of the vena cava infe-
rior is carried to the right auricle of the heart, and instead of
passing from there into the right ventricle, as in the case of
the adult heart, it goes directly into the left auricle by means

of an opening in the auricular septum, known as the *foramen ovale.* The flow of blood from the inferior vena cava through the foramen ovale and into the left auricle is facilitated by the fact that the inferior vena cava points almost directly into the foramen ovale. The Eustachian valve, consisting of a crescentic fold of fibrous tissue covered with endocardium and extending from a point between the opening of the superior and inferior venæ cavæ over to the lower and anterior margin of the foramen ovale, also favors this peculiar course of the blood. The base of the fold lies on the right auriculoventricular ring, and the concavity of the fold is directed upward. From its position the Eustachian valve acts as a guiding groove or gutter for passing the blood from the inferior vena cava to the foramen ovale. On entering the left auricle the blood is passed into the left ventricle and thence into the aorta, to be distributed all over the body, but principally to the head and upper extremities. From the latter regions the blood returns to the heart by the superior vena cava. On entering the right auricle the blood from the superior vena cava passes in front of the stream that flows from the inferior vena cava to the foramen ovale, and enters the right ventricle. The direction in which the superior vena cava points (toward the auriculoventricular ring), and also the Eustachian valve, are the factors that determine the separation of the two streams. On entering the right ventricle the blood from the superior vena cava is forced into the pulmonary artery toward the lungs. Before reaching the lungs this blood meets with a channel of communication between the pulmonary artery and the aorta (ductus arteriosus), into which the larger portion of the blood from the pulmonary artery enters and mingles with the blood of the aorta; the remainder passes along the pulmonary artery to the structure of the lungs, which it nourishes, and thence back to the left auricle by means of the pulmonary veins.

The blood in the aorta that comes from the left ventricle passes largely to the head, but that which enters from the ductus arteriosus largely passes into the descending aorta. On passing down the descending aorta, some of the blood enters the mesenteric arteries, and thence back to the venous circulation by means of the portal vein and the liver. Some of the blood enters the iliac arteries and nourishes the lower extremities;

but the major part of the blood leaves the fetal body by the hypogastric arteries. The hypogastric arteries are branches of the internal iliacs, and course along the abdomen to leave the fetal body at the umbilicus, where on emerging they change their names to umbilical arteries and proceed to the placenta.

The liver, receiving the freshest blood (from the umbilical vein), is the best nourished of all the organs of the fetus. The result is that the fetal liver is vastly larger in proportion than the adult liver. The branches of the aorta given off to the head and upper extremities distribute blood from the inferior vena cava, while the ductus arteriosus, carrying the blood from the superior cava and right ventricle, enters the aorta in such a way that most of its blood is sent to the lower extremities, abdominal organs, and umbilical arteries. In this way the deoxidized blood is sent back to the placenta for the renewal of its oxygen. The lower extremities are less developed than the upper. There are two reasons for this:

1. The blood contains less oxygen and nourishment.

2. The internal iliac arteries, giving off the umbilical arteries, divert a considerable portion of the blood supply from the external iliacs which go to the lower extremities.

Owing to the ductus arteriosus, but little blood goes to the lungs. The amount is sufficient, however, to keep up the nutrition of the lungs, and they have no function before birth.

The *respiratory centre* in the medulla, which has been quiescent because it has been well supplied with oxygenated blood, is awakened as soon as the connection with the uterine sinuses is interrupted. As soon as the supply of CO_2 rises to a certain point, an impulse of inspiration is generated, and as the infant breathes the lungs assume a condition of partial expansion. With diminished resistance in the expanded lungs the amount of blood in the pulmonary circulation increases, and as the amount passing through the *ductus arteriosus* consequently decreases, this soon is obliterated. At the same time the amount of blood returning to the left auricle increases in quantity, and the intra-auricular pressure becomes greater; then, too, the inferior vena cava sends less blood, for the ductus venosus no longer carries the blood from the placental circulation, and, therefore, the foramen ovale is not used, and is soon closed by the adhesion of its valve-like curtain. Thus, the adult circulation is established

in place of the fetal circulation in consequence of respiratory movements. Owing to the division and occlusion of the umbilical cord, blood no longer passes through the umbilical vessels, with the result that the umbilical vein degenerates into a fibrous cord (round ligament of the liver). The hypogastric arteries remain pervious for the first part of their course, as the superior vesical arteries; but the remainder of their course is obliterated and degenerates into fibrous cords.

The *period of gestation* during which the embryo is developing in the uterus may be put at 280 days, and probably dates from the first day of the last menstruation. Owing to the difficulty of knowing the time of fertilization, the exact period is not known. One of the earliest, and most obvious and most usual, signs of pregnancy is the cessation of menstruation. The *cause* of the *expulsion* of the fetus from the uterus is not well known, and it is probable that on account of the exceedingly irritable condition of the uterus a number of causes may exist. Among these have been suggested the pressure on the tissue of the uterus or on the ganglia of the cervix, and the gradually increasing venosity of the fetal blood.

The frequency of *multiple conceptions* is for twins, at a ratio of 1 to 120; for triplets, 1 to 7910; and for quadruplets, 1 to 371,126 births. *Twins* may arise from separate eggs or from a single egg. The presence of a double chorion is diagnostic of the former, and a single chorion of the latter. The separate ova may come from a single Graafian follicle or not. When the offspring come from separate ova, they may be of separate sexes, and do not necessarily resemble one another; but whenever they come from the same ovum, by a separation of the blastomeres, they are of the same sex, and their personal resemblance is very great.

The *factors* that *determine sex* are very little understood. As a general rule, more boys are born than girls. The sexual organs are differentiated at the eighth week of uterine life, but the trend of modern opinion seems to be that sex is determined in the germ cells at or before fertilization.

1. In certain worms, eggs of two sizes are produced, of which, the large ones, after fertilization, develop always into females, the small ones into males.

2. In some invertebrates parthenogenesis forms the only method of reproduction, and the individuals formed are all females. But in other species where fertilization occasionally takes place the parthenogenetic eggs become either males or females.

3. In man of all twins born there are two kinds. Those that are developed from two different eggs, each having its own chorion and developing its own placenta. These are designated as false twins and in sex may be either male or female, or male and female. In true or identical twins, the two are developed from a single ovum and are included in a single chorion. They are either both males or both females.

4. In some insects the determination of sex is correlated with a visible difference in the chromosomes of the spermatozoön. In some cases one-half of the spermatozoa contain an unpaired or accessory chromosome. Those showing this structure produce females, while all others give rise to males. In other cases all the spermatozoa exhibit the same number of chromosomes, but one-half of them contain a large "idiochromosome," the other half a small one. The former give rise to females, the latter to males. Sex, therefore, seems to depend upon which of the sex-determining structures in the two cells predominates after union. It may, moreover, be said that the production of sex is self-regulating, insomuch that a scarcity of the sex of one kind tends to a production of individuals of that sex.

QUESTIONS ON CHAPTER XIV

What is reproduction?
How many methods are there?
Describe the asexual method.
Why does a growing mass of protoplasm divide?
What is the essential fact of sexual reproduction?
Describe various stages in the development of sexual reproduction.
What are the primary and secondary sexual characters?
Describe the development of a spermatozoön.
What difference is there between the sexual elements?
What is the rate of movement of a spermatozoön?
What is semen?
What is meant by the maturation of the ovum?
What is a Graafian follicle?
Describe ovulation.
How does the ovum reach the uterus?
What is fertilization? Where does it take place?
Describe the process and development of menstruation.

How long does menstruation last? What are the symptoms accompanying it?

Give the physiological causes of menstruation.

Discuss puberty.

What is the menopause?

What is the object of menstruation?

What is the relation of ovulation to menstruation?

How do spermatozoa reach the Fallopian tubes?

How many types of fetal circulation are there?

Describe the placental circulation.

What changes take place in fetal circulation at birth?

What is the length of the period of gestation in the human being? From what time does it probably date?

What is the earliest sign of pregnancy?

What is the cause of the expulsion of the fetus from the uterus?

Discuss the occurrence of twins.

Discuss the determination of sex.

Is the production of sex self-regulating?

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